

2003

# Palladium approaches to beta- and gamma-carbolines

Haiming Zhang  
*Iowa State University*

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**Palladium approaches to beta- and gamma-carbolines**

**by**

**Haiming Zhang**

**A dissertation submitted to the graduate faculty  
in partial fulfillment of the requirements for the degree of**

**DOCTOR OF PHILOSOPHY**

**Major: Organic Chemistry**

**Program of Study Committee:  
Richard C. Larock (Major Professor)  
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**Iowa State University  
Ames, Iowa**

**2003**

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**Major Professor**

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**For the Major Program**

To my wife, Ye Gu

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**LIST OF ABBREVIATIONS**

<b>Ac</b>	<b>acetyl</b>
<b>aq</b>	<b>aqueous</b>
<b>Bn</b>	<b>benzyl</b>
<b>br s</b>	<b>broad singlet</b>
<b><i>n</i>-Bu</b>	<b>butyl</b>
<b><i>t</i>-Bu</b>	<b><i>tert</i>-butyl</b>
<b>cat.</b>	<b>catalytic</b>
<b>d</b>	<b>doublet</b>
<b>dba</b>	<b>dibenzylideneacetone</b>
<b>dd</b>	<b>doublet of doublets</b>
<b>dt</b>	<b>doublet of triplets</b>
<b>DMF</b>	<b><i>N,N</i>-dimethylformamide</b>
<b>DMSO</b>	<b>dimethyl sulfoxide</b>
<b>eq</b>	<b>equation</b>
<b>equiv</b>	<b>equivalent</b>
<b>Et</b>	<b>ethyl</b>
<b>h</b>	<b>hour(s)</b>
<b>HRMS</b>	<b>high resolution mass spectroscopy</b>
<b>Hz</b>	<b>Hertz</b>
<b>IR</b>	<b>infrared</b>
<b>m</b>	<b>multiplet</b>

<b>Me</b>	<b>methyl</b>
<b>mL</b>	<b>milliliter(s)</b>
<b>mol</b>	<b>mole(s)</b>
<b>MOM</b>	<b>methoxymethyl</b>
<b>mp</b>	<b>melting point</b>
<b>Ms</b>	<b>methanesulfonyl</b>
<b>MS</b>	<b>mass spectrometry</b>
<b>NMR</b>	<b>nuclear magnetic resonance</b>
<i><b>o</b></i>	<b>ortho</b>
<i><b>p</b></i>	<b>para</b>
<b>Ph</b>	<b>phenyl</b>
<i><b>n</b></i> -Pr	<b>propyl</b>
<b>q</b>	<b>quartet</b>
<b>s</b>	<b>singlet</b>
<b>satd</b>	<b>saturated</b>
<b>t</b>	<b>triplet</b>
<b>TBAC</b>	<b>tetra-<i>n</i>-butylammonium chloride</b>
<i><b>tert</b></i>	<b>tertiary</b>
<b>THF</b>	<b>tetrahydrofuran</b>
<b>TLC</b>	<b>thin-layer chromatography</b>
<b>TMS</b>	<b>trimethylsilyl</b>
<b>Ts</b>	<b><i>p</i>-toluenesulfonyl</b>

**ABSTRACT**

A variety of substituted  $\beta$ - and  $\gamma$ -carbolines containing aryl, alkyl, hydroxymethyl, ester and silyl functionality at the 3- and 4-positions have been prepared by the palladium-catalyzed iminoannulation of internal and terminal alkynes. This methodology has been successfully employed to the synthesis of two biologically active  $\beta$ -carboline alkaloids, ZK93423 and abecarnil.

A variety of 3-substituted  $\beta$ - and  $\gamma$ -carbolines have been synthesized from *N*-substituted 3-iodo-1*H*-indole-2-carboxaldehydes and 2-bromo-1*H*-indole-3-carboxaldehydes, respectively. The coupling of these aldehydes with various terminal acetylenes using cat.  $\text{PdCl}_2(\text{PPh}_3)_2/\text{CuI}$  readily affords the corresponding alkynylindole carboxaldehydes, which have subsequently been converted to the corresponding *tert*-butylimines and cyclized to  $\beta$ - and  $\gamma$ -carbolines by either copper-catalyzed or thermal processes.

A variety of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various  $\gamma$ -carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields. This "intramolecular" concept has been extended to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

A novel 1,4-palladium migration has been observed by trapping the palladium intermediate generated from *o*-iodobiaryls by way of a Suzuki coupling reaction. The choice of reaction conditions is important in turning "on" and "off" the migration. There are important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products.

## GENERAL INTRODUCTION

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as  $\beta$ - and  $\gamma$ -carbolines, respectively, are the key structural units for a variety of biologically important alkaloids. Numerous  $\beta$ -carbolines possess potent and varied CNS and anticancer activity, and  $\gamma$ -carbolines have been studied extensively as antitumor agents. The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity. The isolation and synthesis of naturally occurring carbolines and the synthesis of  $\beta$ - and  $\gamma$ -carboline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance.

Palladium-catalyzed annulation processes have recently proven to be a powerful method for the construction of a wide variety of hetero- and carbocycles in the Larock group. In addition, a variety of hetero- and carbocycles have been successfully synthesized by the copper-catalyzed, the palladium-catalyzed and the electrophile-induced cyclization of alkynes having a *tert*-butylimino group in close proximity to the carbon-carbon triple bond. In this dissertation, palladium-catalyzed intermolecular and intramolecular annulation, and palladium/copper-catalyzed coupling and cyclization of alkynes have been investigated and developed into efficient synthetic methods for the construction of  $\beta$ - and  $\gamma$ -carbolines.

Palladium has been shown to catalyze an extraordinary number of incredibly diverse reactions, making it one of the most useful of all metals for organic synthesis. With the exception of alkene, alkyne and carbon monoxide insertion reactions, the palladium moiety typically stays directly attached to the carbon to which it is originally introduced. However, one of the unique features of palladium is its ability to migrate from one carbon to another. The Larock group has recently observed a number of novel palladium migration reactions. In this dissertation, a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids has been investigated.

## Dissertation Organization

This dissertation is divided into four chapters. Each chapter is a journal paper presented with its own introduction, results and discussion, experimental section, conclusions, acknowledgment and references.

Chapter 1 describes the synthesis of 3,4-disubstituted and 3-substituted  $\beta$ - and  $\gamma$ -carbolines by the palladium-catalyzed iminoannulation of internal and terminal alkynes, respectively, and its application to the synthesis of two biologically active  $\beta$ -carboline alkaloids, ZK93423 and abecarnil. The regioselectivity issues are discussed and the scope and limitations of this methodology are explored.

Chapter 2 describes the synthesis of 3-substituted  $\beta$ - and  $\gamma$ -carbolines by the palladium/copper-catalyzed coupling and cyclization of terminal alkynes. The scope and limitations of this methodology are explored and mechanisms for these transformations are proposed.

Chapter 3 extends the palladium-catalyzed iminoannulation chemistry to intramolecular iminoannulation to synthesize a variety of annulated  $\gamma$ -carbolines. This intramolecular iminoannulation is mechanistically related to the process examined in Chapter 1, but results in the formation of  $\gamma$ -carbolines with an additional ring fused across the 4- and 5-positions. The extension of this "intramolecular" concept to other palladium-catalyzed annulations to synthesize various complex heteroatom-containing polycycles is also examined.

Chapter 4 describes a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids. Important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products, are discussed.

Finally, a general conclusion to this dissertation and acknowledgments are presented, and the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all previously unknown starting materials and palladium-catalyzed reaction products are provided in Appendices A-D.

## CHAPTER 1. SYNTHESIS OF $\beta$ - AND $\gamma$ -CARBOLINES BY THE PALLADIUM-CATALYZED IMINOANNULATION OF ALKYNES

A paper published in the *Journal of Organic Chemistry*

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### Abstract

A variety of substituted  $\beta$ - and  $\gamma$ -carbolines have been prepared in moderate to excellent yields by the palladium-catalyzed annulation of internal and terminal acetylenes by the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes, respectively. This annulation chemistry is effective for a wide range of alkynes, including aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl-, and trimethylsilyl-substituted alkynes. When an unsymmetrical internal alkyne is employed, this method generally gives two regioisomers. When a terminal alkyne is employed, only one regioisomer has been isolated. This palladium-catalyzed annulation chemistry has also been successfully applied to the synthesis of two biologically interesting  $\beta$ -carboline alkaloids, ZK93423 and abecarnil (ZK112119).

### Introduction

Pyrido[3,4-*b*]indoles<sup>1</sup> and pyrido[4,3-*b*]indoles,<sup>2</sup> commonly known as  $\beta$ - and  $\gamma$ -carbolines, respectively, are the key structural units for a variety of biologically important alkaloids. For example, numerous  $\beta$ -carbolines possess potent and varied CNS and anticancer activity,<sup>1</sup> and  $\gamma$ -carbolines have been studied extensively as antitumor agents.<sup>3</sup> The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity.<sup>3</sup> The isolation and synthesis of naturally occurring carbolines and the synthesis of  $\beta$ - and  $\gamma$ -carboline

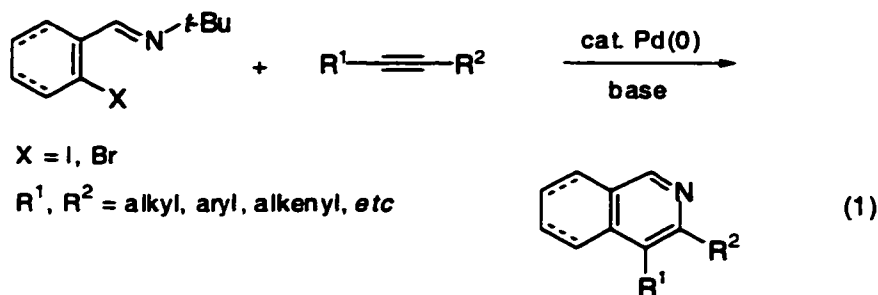
derivatives have received considerable attention in the literature<sup>1,2,4</sup> due to their biological and pharmaceutical importance.

Carboline heterocycles have been synthesized by employing palladium methodology. For instance, a combination of palladium-catalyzed cross-coupling and base-promoted intramolecular nucleophilic aromatic substitution generates the  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -carboline parent systems.<sup>5</sup> This strategy has been successfully applied to the synthesis of eudistomin T, a  $\beta$ -carboline alkaloid.<sup>6</sup> A combination of palladium-catalyzed amination and arylation reactions has also been developed to synthesize the carboline parent systems.<sup>4a</sup> A palladium-mediated intramolecular amination, which produces substituted  $\beta$ -carbolines as important intermediates for the total synthesis of lavendamycin methyl ester, has been reported by Boger.<sup>7</sup> This synthesis has the disadvantage of using more than one equivalent of the palladium reagent. Recently,  $\beta$ - and  $\gamma$ -carbolines have also been synthesized by a combination of palladium-catalyzed coupling, imine/oxime formation and cyclization.<sup>4c,f-k</sup> Employing this chemistry, Hibino has synthesized several naturally occurring  $\beta$ -carbolines.<sup>4f,h</sup>

Annulation processes have proven very useful in organic synthesis due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology<sup>8</sup> can be effectively employed for the synthesis of indoles,<sup>9</sup> isoindolo[2,1-a]indoles,<sup>10</sup> benzofurans,<sup>11</sup> benzopyrans,<sup>11</sup> isocoumarins,<sup>11,12</sup>  $\alpha$ -pyrones,<sup>12,13</sup> indenones,<sup>14</sup> and polycyclic aromatic hydrocarbons.<sup>15</sup>

Recently, we have developed a general synthesis of isoquinolines and pyridines by the palladium-catalyzed iminoannulation of internal alkynes (eq 1).<sup>16</sup> Our own interest in extending this type of iminoannulation reaction prompted us

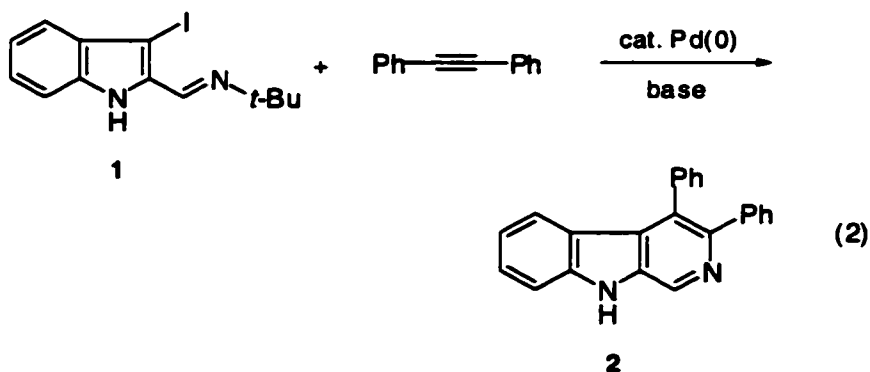




to examine potential applications to the synthesis of a wide variety of  $\beta$ - and  $\gamma$ -carbolines. A brief communication on this work has been previously reported.<sup>17</sup> Herein, we wish to report the full details of this palladium-catalyzed annulation of internal alkynes for the synthesis of various  $\beta$ - and  $\gamma$ -carbolines, extension of this methodology to terminal alkynes, and applications to the synthesis of two biologically active  $\beta$ -carboline alkaloids ZK93423<sup>18</sup> and abecarnil (ZK112119).<sup>19</sup>

## Results and Discussion

Our initial studies focused on the palladium-catalyzed iminoannulation of internal alkynes employing the *tert*-butylimine of 3-iodo-1*H*-indole-2-carboxaldehyde (1). The reaction of diphenylacetylene and imine 1 was chosen as the model system for optimization (eq 2). In the early stages of this work, the reaction conditions



examined were similar to the conditions employed in our earlier isoquinoline synthesis.<sup>16</sup> For example, the reactions were run with 0.25 mmol of the *tert*-butylimine, 2 equiv of diphenylacetylene, 5 mol % of  $\text{Pd}(\text{OAc})_2$ , 10 mol % of  $\text{PPh}_3$  and 1 equiv of  $\text{Na}_2\text{CO}_3$  as a base in 5 mL of DMF at 100 °C (Table 1, entry 1).

**Table 1. Optimization of the Palladium-Catalyzed Formation of 3,4-Diphenyl- $\beta$ -carboline (eq 2)**

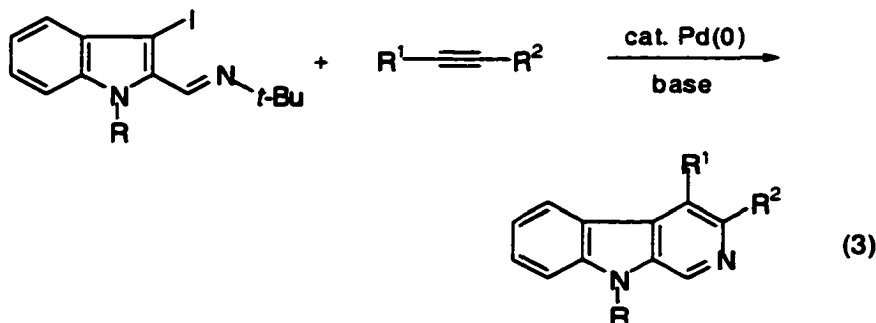
entry	catalyst	% catalyst	% PPh <sub>3</sub>	base (equiv)	temp (°C), time (h)	% isolated yield of 2
1	Pd(OAc) <sub>2</sub>	5	10	Na <sub>2</sub> CO <sub>3</sub> (1)	100, 48	0
2	Pd(OAc) <sub>2</sub>	5	10	Na <sub>2</sub> CO <sub>3</sub> (1)	130, 48	0
3	Pd(OAc) <sub>2</sub>	5	10	K <sub>2</sub> CO <sub>3</sub> (1)	100, 48	0
4	Pd(OAc) <sub>2</sub>	5	10	Cs <sub>2</sub> CO <sub>3</sub> (1)	100, 48	0
5	Pd(OAc) <sub>2</sub>	5	10	NaOAc (1)	100, 48	0
6	Pd(OAc) <sub>2</sub>	5	10	KOAc (1)	100, 48	0
7	Pd(OAc) <sub>2</sub>	5	10	Pyridine (1)	100, 48	0
8	Pd(OAc) <sub>2</sub>	5	10	DTBMP <sup>a</sup> (1)	100, 48	0
9	Pd(OAc) <sub>2</sub>	5	10	NEt <sub>3</sub> (1)	100, 24	39
10	Pd(OAc) <sub>2</sub>	5	10	<i>i</i> -Pr <sub>2</sub> NEt (1)	100, 24	40
11	Pd(OAc) <sub>2</sub>	5	10	Cy <sub>2</sub> NEt (1)	100, 50	48
12	Pd(OAc) <sub>2</sub>	5	10	<i>n</i> -Bu <sub>3</sub> N (1)	100, 24	48
13	Pd(OAc) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	54
14	Pd(OAc) <sub>2</sub>	5	2.5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	45
15	Pd(OAc) <sub>2</sub>	10	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 8	51
16	Pd(OAc) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (2)	100, 10	52
17	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	40
18	PdCl <sub>2</sub> (PhCN) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	46
19	Pd(PPh <sub>3</sub> ) <sub>4</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	41
20	Pd(dba) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	41
21	Pd(dppe) <sub>2</sub>	5	5	<i>n</i> -Bu <sub>3</sub> N (1)	100, 10	51

<sup>a</sup> 2,6-Di-*tert*-butyl-4-methylpyridine.

However, these conditions failed to produce any of the desired  $\beta$ -carboline **2**. When the reaction temperature was raised to 130 °C, still no desired product was detected after 48 h (entry 2). We next examined different inorganic bases in the reaction, since the nature of the base often has a dramatic effect on these palladium-catalyzed annulation reactions.<sup>8</sup> All of the inorganic bases we tried, including K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, NaOAc, and KOAc proved to be ineffective (entries 3-6). Two pyridine bases, namely pyridine and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) also failed to produce any of the desired product (entries 7 and 8). When the tertiary amine base triethylamine was employed, a 39% yield of the desired product was isolated (entry 9). Several other tertiary amine bases, including *N,N*-diisopropylethylamine (*i*-Pr<sub>2</sub>NEt), *N*-ethyldicyclohexylamine (Cy<sub>2</sub>NEt), and tri-*n*-butylamine (*n*-Bu<sub>3</sub>N) generated the desired product, but in relatively low yields (entries 10-12). Comparing entries 11 and 12, we noticed that the use of *n*-Bu<sub>3</sub>N required not only shorter reaction times, but also produced a cleaner reaction as monitored by TLC analysis than the use of Cy<sub>2</sub>NEt. Therefore, we selected *n*-Bu<sub>3</sub>N as the base of choice for the succeeding optimization work. We next changed the amount of PPh<sub>3</sub> ligand. When 5 mol % of PPh<sub>3</sub> was employed in the reaction, a slight increase in the yield, as well as a reduction in the reaction time, was observed (entry 13). Further reduction in the amount of PPh<sub>3</sub> to 2.5 mol % was accompanied by a decrease in the product yield (entry 14). Additional attempts to optimize this annulation process employed 5 mol % of PPh<sub>3</sub>, but varied either the amount of Pd(OAc)<sub>2</sub> (entry 15) or *n*-Bu<sub>3</sub>N (entry 16). A slight decrease in the product yield was observed in both cases. Finally, 5 mol % of five different palladium catalysts other than Pd(OAc)<sub>2</sub> were employed, but none of these reactions gave a yield higher than 54% (entry 13, where 5 mol % of Pd(OAc)<sub>2</sub>, 5 mol % of PPh<sub>3</sub> and 1 equiv of *n*-Bu<sub>3</sub>N were employed).

It has been reported that aryl halides and indole can undergo palladium-catalyzed amination to produce *N*-arylindoles.<sup>20</sup> The low yields of carboline observed under various reaction conditions may be a result of the *N*-arylation of our

N–H containing indole by another molecule of starting material to form a dimer, which may subsequently form oligomers or polymers. However, no direct evidence has been obtained during the course of our study to support this hypothesis. The easiest way to solve this problem is to employ *N*-protected indole imines. 3-Iodo-1-methylindole-2-methylene-*tert*-butylamine (**3**) was, therefore, prepared and allowed to react with diphenylacetylene under the optimal reaction conditions for the annulation of diphenylacetylene by imine **1** (Table 1, entry 13; Conditions A in Table 2). As we expected, a substantial 76% yield of the desired  $\beta$ -carboline **4** was observed (Table 2, entry 1). It is worth noting that when the conditions in our earlier isoquinoline synthesis<sup>16</sup> were employed, the same reaction afforded the desired product, but in a lower yield. When imine **3** and ethyl 3-phenylpropiolate are employed, the annulation reaction gives two isomers **5** and **6** in 58% and 42% isolated yields, respectively (Table 2, entry 3). Thus, we have chosen Conditions A as our general reaction procedure for the synthesis of  $\beta$ -carbolines, instead of further endlessly optimizing the reaction conditions. We then proceeded to determine the scope and limitations of this methodology by annulating a wide variety of acetylenes with imine **3** and other *N*-substituted indole imines (eq 3). The results of this study are summarized in Table 2.



The annulation of a variety of internal alkynes with imine **3** under Conditions A has afforded the desired  $\beta$ -carbolines in moderate to excellent yields (entries 1, 2, 4, 6-8, 10-13, 15 and 16). When an unsymmetrical alkyne is employed, two regioisomers have generally been observed, usually with poor regioselectivity

**Table 2. Synthesis of  $\beta$ -Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 3)<sup>a</sup>**

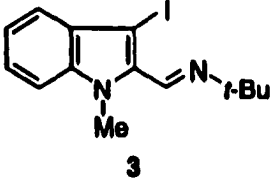
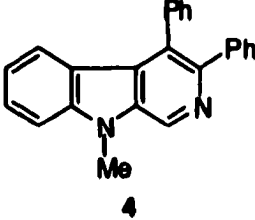
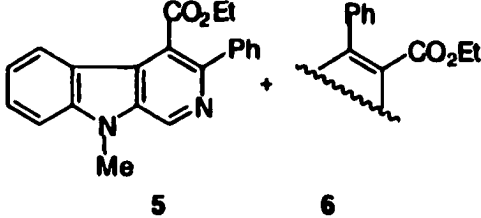
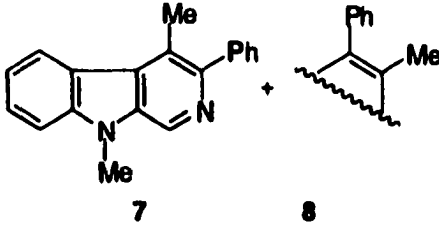
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1		$\text{Ph} \equiv \text{Ph}$	A	4		76
2		$\text{Ph} \equiv \text{CO}_2\text{Et}$	A	5		58 + 42
3			B	17		99 + trace
4		$\text{Ph} \equiv \text{Me}$	A	5		49 + 42
5			B	6		64 + 22

Table 2. Continued

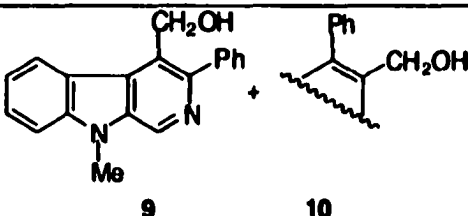
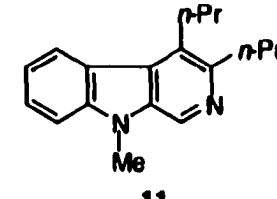
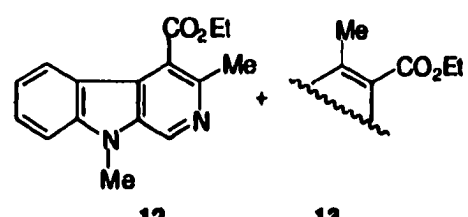
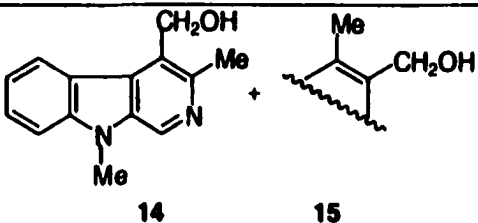
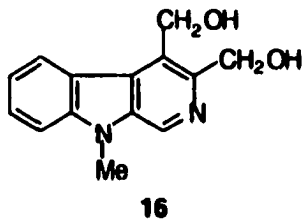
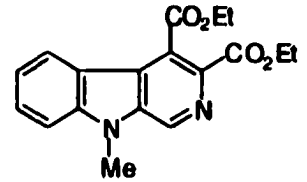
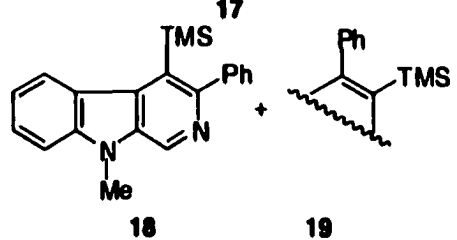
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
6		$\text{Ph} \equiv \text{CH}_2\text{OH}$	A	2	 <div style="display: flex; justify-content: space-around; width: 100%;"> <span>9</span> <span>10</span> </div>	43 + 36
7		$n\text{-Pr} \equiv n\text{-Pr}$	A	2	 <div style="text-align: center;">11</div>	72
8		$\text{Me} \equiv \text{CO}_2\text{Et}$	A	2	 <div style="display: flex; justify-content: space-around; width: 100%;"> <span>12</span> <span>13</span> </div>	73 (1:1) <sup>b</sup>
9			B	22		62 (1:1.7) <sup>b</sup>

Table 2. Continued

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
10		$\text{Me} \equiv \text{CH}_2\text{OH}$	A	2	 <div style="display: flex; justify-content: space-around;"> <span>14</span> <span>15</span> </div>	100 (1:1) <sup>b</sup>
11		$\text{HOCH}_2 \equiv \text{CH}_2\text{OH}$	A	2	 <div style="text-align: center;">16</div>	96
12		$\text{EtO}_2\text{C} \equiv \text{CO}_2\text{Et}$	A	9	 <div style="text-align: center;">17</div>	49
13		$\text{Ph} \equiv \text{TMS}$	A	1.5	 <div style="display: flex; justify-content: space-around;"> <span>18</span> <span>19</span> </div>	34 + 25

**Table 2. Continued**

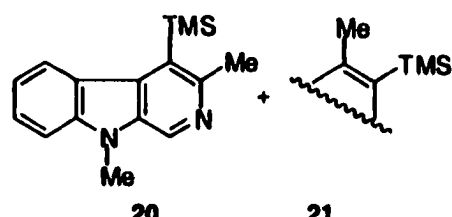
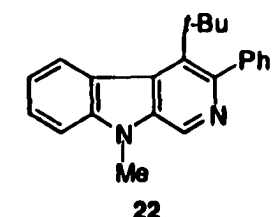
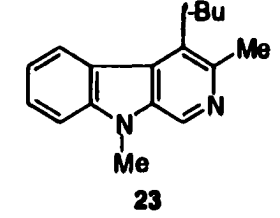
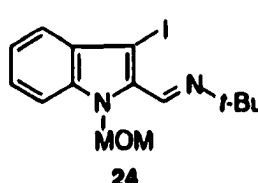
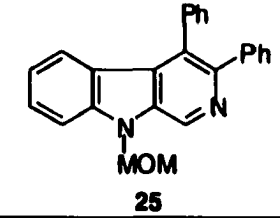
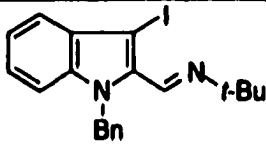
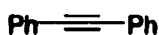
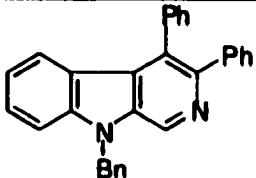
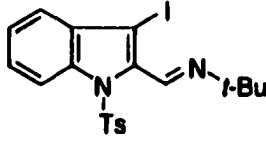
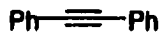
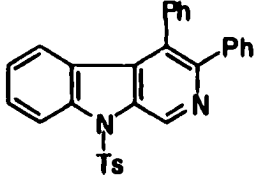
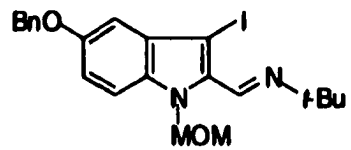
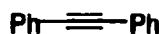
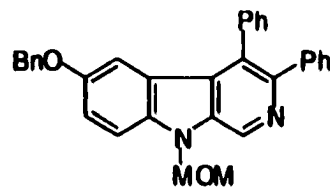
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
14			B	24		31 + 24
15		$\text{Me} \equiv \text{TMS}$	A	1.5	 <div style="display: flex; justify-content: space-around;"> <span>20</span> <span>21</span> </div>	31 + 22
16		$\text{Ph} \equiv t\text{-Bu}$	A	1	 <div style="text-align: center;">22</div>	32
17		$\text{Me} \equiv t\text{-Bu}$	A	2	 <div style="text-align: center;">23</div>	trace
18	 <div style="text-align: center;">24</div>	$\text{Ph} \equiv \text{Ph}$	A	3	 <div style="text-align: center;">25</div>	80



Table 2. Continued

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
19	 <b>26</b>		A	5	 <b>27</b>	100
20	 <b>28</b>		A	5	 <b>29</b>	32
21	 <b>30</b>		A	1	 <b>31</b>	79

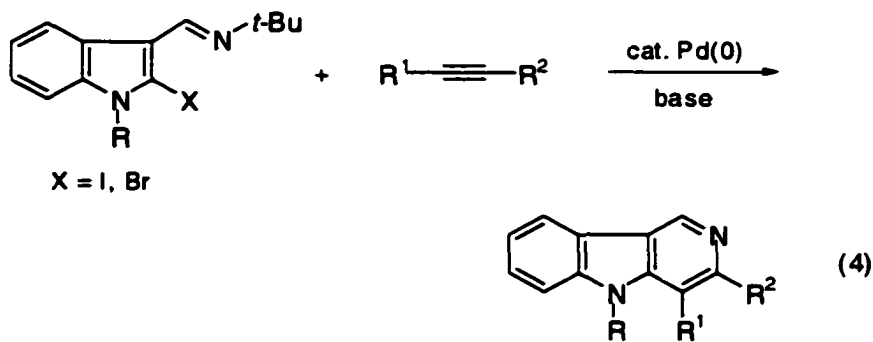
<sup>a</sup>Representative procedure for Conditions A: 5 mol % Pd(OAc)<sub>2</sub>, 5 mol % PPh<sub>3</sub>, *n*-Bu<sub>3</sub>N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions B: TBAC (0.25 mmol) was added to Conditions A. <sup>b</sup>The ratio was determined by <sup>1</sup>H NMR spectroscopic analysis.

(entries 2, 4, 6-8, 10, 11, 13 and 15). These results are consistent with our isoquinoline synthesis in which two regioisomers were also observed when an electron-rich imine was employed.<sup>16</sup> Interestingly, the poor regioselectivity can often be improved by simply adding 1 equiv of *n*-Bu<sub>4</sub>NCl (TBAC) (Conditions B, also see the latter mechanistic discussion). For example, the annulation of imine **3** with ethyl 3-phenylpropionate under Conditions B gave predominantly a single isomer (entry 3). The regioselectivity of reactions of imine **3** with 1-phenylpropyne and ethyl 2-butyrate improved from around 1:1 to about 3:1 and 2:1, respectively (entries 5 and 9). However, the regioselectivity of the annulation of phenyl(trimethylsilyl)acetylene by imine **3** under Conditions B remained essentially unchanged (compare entries 13 and 14). Therefore, the use of TBAC is not generally applicable for increasing the regioselectivity of this chemistry, which is believed to be highly sensitive to the nature of the internal alkyne. The annulation results from the reactions of phenyl(trimethylsilyl)acetylene or 1-trimethylsilyl-1-propyne and imine **3** (entries 13 and 15) were quite interesting, since these alkynes produced unexpected carboline products bearing the more hindered trimethylsilyl group in the 4-position as the major isomers, while the same alkynes afforded desilylated mono-substituted products in our isoquinoline synthesis.<sup>16</sup> This annulation chemistry also works on an alkyne bearing a bulky *tert*-butyl group. For example, 3,3-dimethyl-1-phenyl-1-butyne, which failed to afford any of the desired product in our isoquinoline synthesis,<sup>16</sup> produces only the unexpected isomer **22** in a 32% yield (entry 16), whose regiochemistry has been confirmed by its NOESY spectrum. When another *tert*-butyl-bearing alkyne, 4,4-dimethyl-2-pentyne, was employed in this annulation chemistry, it produced only a trace of the carboline product (entry 17). Quite possibly, the low boiling point of 4,4-dimethyl-2-pentyne (82 °C) results in loss of the acetylene from the reaction vessel under the reaction conditions and thus lowers the yield significantly.

Three other *N*-substituted indole imines were also employed in this palladium-catalyzed iminoannulation chemistry. The annulation of diphenylacetylene by the *N*-

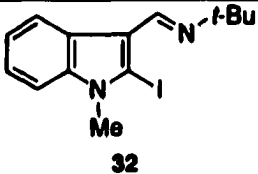
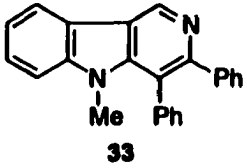

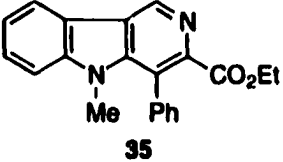
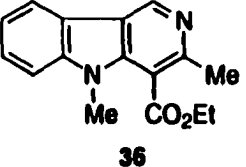
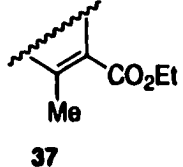
methoxymethyl-, *N*-benzyl-, and *N*-tosyl-substituted imines **24**, **26**, and **28** under Conditions A afforded 80%, 100% and 32% yields of the desired products, respectively (entries 18-20). Finally, the annulation of diphenylacetylene by the 1-methoxymethyl-5-benzyloxy-substituted imine **30** under Conditions A was carried out, which generated the desired  $\beta$ -carboline **31** in a 79% yield (entry 21).

Encouraged by our success with the synthesis of  $\beta$ -carbolines, we have also investigated the palladium-catalyzed iminoannulation of internal acetylenes using 2-haloindole-3-methylene-*tert*-butylamines in order to synthesize substituted  $\gamma$ -carbolines (eq 4). The results of this investigation are summarized in Table 3.

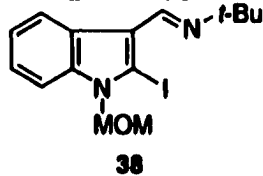
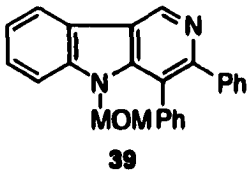
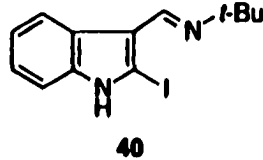
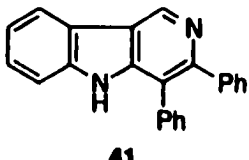
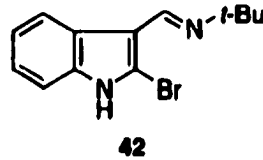
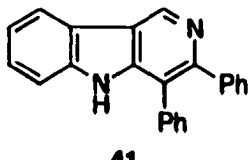
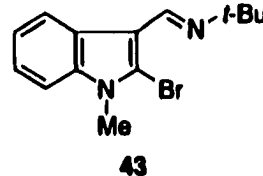
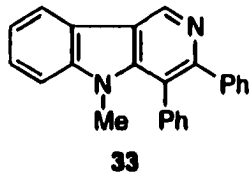


The annulation reaction of the *tert*-butylimine of 2-iodo-1-methylindole-3-carboxaldehyde (**32**) and diphenylacetylene under Conditions A, which were quite successful in our  $\beta$ -carboline synthesis, was first examined. To our surprise, this reaction did not afford any of the desired product **33** (entry 1), but a 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was obtained instead. This product apparently arises from the hydrolysis of 1-methylindole-3-methylene-*tert*-butylamine during the work-up. When 4-octyne was employed under the same reaction conditions, none of the desired product was observed either. Instead, the same reduced product was isolated in a 76% yield (entry 3). When the standard reaction conditions in our isoquinoline synthesis,<sup>16</sup> Conditions C, were employed in the annulation of diphenylacetylene by imine **32**, a messy reaction was observed and only a 24% yield of the desired product was obtained (entry 2). Surprisingly, the reaction of imine **32** with 4-octyne under Conditions C afforded a 78% yield of the

**Table 3. Synthesis of  $\gamma$ -Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 4)<sup>a</sup>**

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1	 32	Ph $\equiv$ Ph	A	24	 33	0 <sup>b</sup>
2			C	48		24
3		<i>n</i> -Pr $\equiv$ <i>n</i> -Pr	A	12	 34	0 <sup>c</sup>
4			C	50		78
5		Ph $\equiv$ CO <sub>2</sub> Et	C	28	 35	72
6		Me $\equiv$ CO <sub>2</sub> Et	C	24	 36           +  37	69 (1:7.5) <sup>d</sup>

**Table 3. Continued**

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
7	 <b>38</b>	$\text{Ph} \equiv \text{Ph}$	C	96°	 <b>39</b>	40
8	 <b>40</b>	$\text{Ph} \equiv \text{Ph}$	C	96	 <b>41</b>	0
9			A	96		68
10	 <b>42</b>	$\text{Ph} \equiv \text{Ph}$	A	50	 <b>41</b>	41
11			C	96		0
12	 <b>43</b>	$\text{Ph} \equiv \text{Ph}$	A	96	 <b>33</b>	30

**Table 3. Continued**

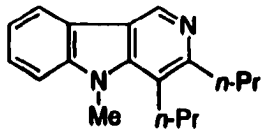
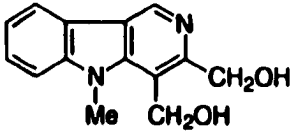
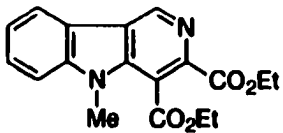
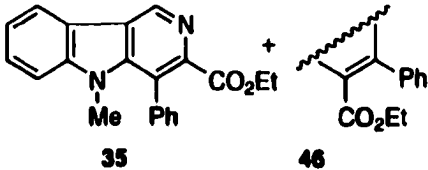
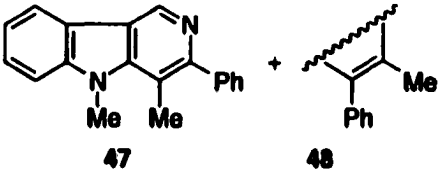
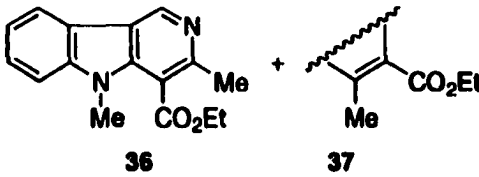
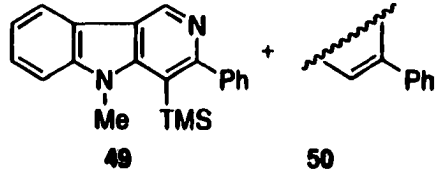
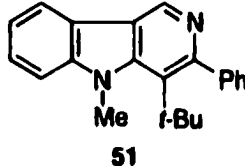
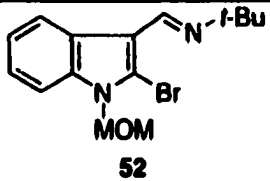

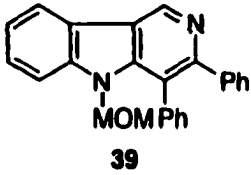
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
13			C	96		58
14			C'	18		70
15		$n\text{-Pr}\text{---}\text{C}\equiv\text{C}\text{---}n\text{-Pr}$	C'	16	 <b>34</b>	67
16		$\text{HOH}_2\text{C}\text{---}\text{C}\equiv\text{C}\text{---}\text{CH}_2\text{OH}$	C'	20	 <b>44</b>	65
17		$\text{EtO}_2\text{C}\text{---}\text{C}\equiv\text{C}\text{---}\text{CO}_2\text{Et}$	C'	24	 <b>45</b>	49
18		$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{CO}_2\text{Et}$	C'	20	 <b>35</b> + <b>46</b>	63 + 37

Table 3. Continued

entry	imine	alkyne	Cond.	time (h)	product(s)	% isolated yield
19		$\text{Ph} \equiv \text{Me}$	C'	20	 47 + 48	49 + 51
20			C	72		44 + 45
21			C <sup>a</sup>	240		50 + 45
22			C <sup>b</sup>	20		29 + 34
23		$\text{Me} \equiv \text{CO}_2\text{Et}$	C'	20	 36 + 37	84 (1:2.4) <sup>d</sup>
24		$\text{Ph} \equiv \text{TMS}$	C'	20	 49 + 50	38 (1:5) <sup>d</sup>
25		$\text{Ph} \equiv t\text{-Bu}$	C'	45	 51	trace

**Table 3. Continued**

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
26	 52	 Ph $\equiv$ Ph	C'	72	 39	70

<sup>a</sup> Representative procedure for Conditions A: 5 mol % Pd(OAc)<sub>2</sub>, 5 mol % PPh<sub>3</sub>, *n*-Bu<sub>3</sub>N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: 10 mol % PPh<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> as the base (0.25 mmol), everything else is the same as in Conditions A. <sup>b</sup> A 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. <sup>c</sup> A 76% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. <sup>d</sup> The ratio was determined by <sup>1</sup>H NMR spectroscopic analysis. <sup>e</sup> The reaction was run at 100 °C for 72 h and subsequently at 125 °C for 24 h. <sup>f</sup> The reaction was run at 125 °C. <sup>g</sup> The reaction was run at 85 °C. <sup>h</sup> 1 Equiv of TBAC was added and the reaction was run at 125 °C.



desired  $\gamma$ -carboline **34** (entry 4). Even more exciting was the observation that the annulation of ethyl 3-phenylpropiolate by imine **32** under Conditions C gave a single regioisomer bearing the phenyl group in the 4-position in a 72% yield (entry 5). When ethyl 2-butynoate was employed, two regioisomers in a 69% total yield, as well as a small amount of the corresponding reduced indolecarboxaldehyde product, were observed (entry 6). Unfortunately, when the alkynes 1-phenylpropyne, 3-phenyl-2-propyn-1-ol, diethyl acetylenedicarboxylate, phenyl(trimethylsilyl)acetylene and 3,3-dimethyl-1-phenyl-1-butyne were employed to this palladium-catalyzed iminoannulation with imine **32**, messy reactions and low yields were observed in all cases.

The annulation of diphenylacetylene by *N*-methoxymethyl-substituted imine **38** took 72 h at 100 °C and subsequently 24 h at 125 °C to reach completion and only 40% of the desired product **39** was isolated. Neither the *N*-benzyl nor the *N*-tosyl-substituted 2-iodoimines afforded any of the desired products when allowed to react with diphenylacetylene under Conditions C. Finally, the annulation reaction of the unsubstituted imine **40** and diphenylacetylene was examined under both Conditions C and A. Surprisingly, Conditions C didn't afford any recognizable product even after 96 h (entry 8). However, Conditions A, which have usually only given the reduced product, afforded a 68% yield of the desired  $\gamma$ -carboline **41** after 96 h (entry 9).

Since the 2-iodoindole imines **32**, **38**, and **40** didn't give very promising results in this palladium-catalyzed iminoannulation chemistry, the corresponding 2-bromoindole imines **42**, **43**, and **52** were prepared in order to examine their iminoannulation chemistry with internal alkynes. The annulation of diphenylacetylene by the unsubstituted 2-bromoindole imine **42** was first examined using Conditions A. This reaction gave the desired  $\gamma$ -carboline **41** in a 41% yield (entry 10). When the same reaction was run using Conditions C, none of the desired product was observed (entry 11). These results are consistent with the results from the annulation of diphenylacetylene by 2-iodoindole imine **40** (compare

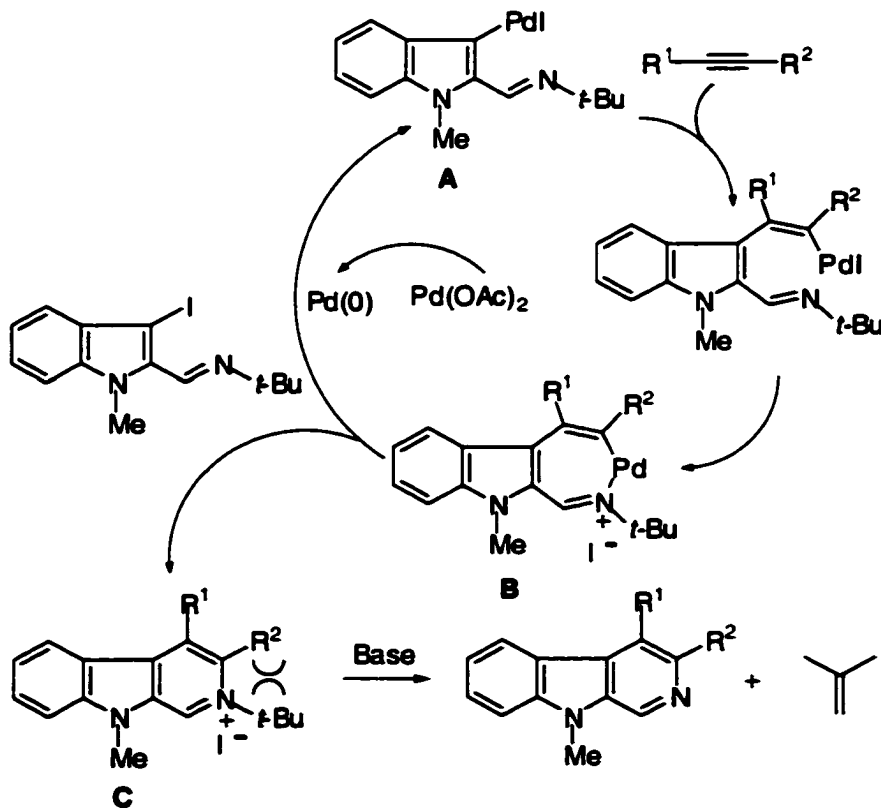
entries 8-11). Interestingly, the annulation of diphenylacetylene by 2-bromo-1-methylindole-3-methylene-*tert*-butylamine (**43**) under Conditions A gave a 30% yield of  $\gamma$ -carboline **33** (entry 12). The same reaction using Conditions C afforded a 58% yield of the desired product after 96 h (entry 13). When the temperature was increased to 125 °C, the reaction was complete in a much shorter time (18 h), producing a 70% yield of  $\gamma$ -carboline **33** (entry 14). Encouraged by this result, we examined the palladium-catalyzed iminoannulation of other internal alkynes by imine **43** under Conditions C at the elevated temperature of 125 °C. Symmetrical alkynes, such as 4-octyne, 2-butyne-1,4-diol, and diethyl acetylenedicarboxylate afforded the desired products in moderate to good yields (entries 15-17). However, when unsymmetrical alkynes were employed, this chemistry generally produced two regioisomers with poor regioselectivity (entries 18, 19, and 23). Ethyl 3-phenyl propiolate produced two regioisomers with the major isomer bearing the phenyl group in the 4-position (entry 18). 1-Phenyl-1-propyne afforded two regioisomers in approximately a 1:1 ratio (entry 19). We tried to improve the regioselectivity of the annulation of 1-phenyl-1-propyne by imine **43**, but none of our attempts gave any improved regioselectivity (entries 20-22). A screening of 88 different combinations of palladium catalysts and bases on this reaction using multiplexed capillary electrophoresis also failed to give reaction conditions, which afford both good regioselectivity and a good yield.<sup>21</sup> The annulation of ethyl 2-butyrate by imine **43** produced a mixture of two regioisomers in an 84% combined yield, with the major isomer having the ester group in the 3-position (entry 23). The reactions of two alkynes bearing sterically bulky groups, phenyl(trimethylsilyl)acetylene and 3,3-dimethyl-1-phenyl-1-butyne were then examined. The former alkyne gave a 1:5 mixture of  $\gamma$ -carboline **49** and its desilylated product **50** in a 38% combined yield (entry 24), and the latter didn't give any of the desired carboline product.

Finally, the *N*-methoxymethyl-substituted 2-bromoindole imine **52** was employed in the annulation of diphenylacetylene. The reaction gave a 70% yield of the desired product **39** (entry 26). It's noteworthy that the reaction of the

corresponding *N*-benzyl-substituted 2-bromoindole imine with diphenylacetylene didn't give a significant yield of the desired product, presumably because of the extra steric hindrance introduced by the benzyl group.

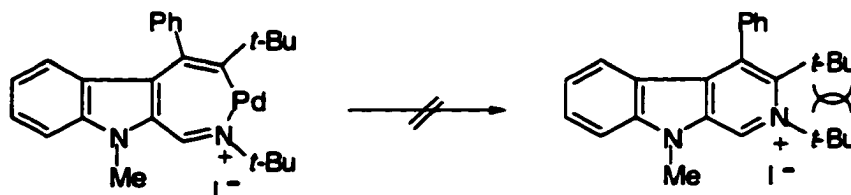
We propose a mechanism for this palladium-catalyzed iminoannulation chemistry, which is similar to our isoquinoline synthesis (Scheme 1).<sup>16</sup> Specifically, oxidative addition of the indole halide to Pd(0) produces an organopalladium intermediate **A**, which then undergoes alkyne insertion, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a 7-membered palladacyclic immonium salt **B**. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt **C** and regenerates the catalyst Pd(0). As previously suggested by Heck,<sup>22</sup> the *tert*-butyl group of the *tert*-butylcarbolinium salt **C** apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.

Scheme 1



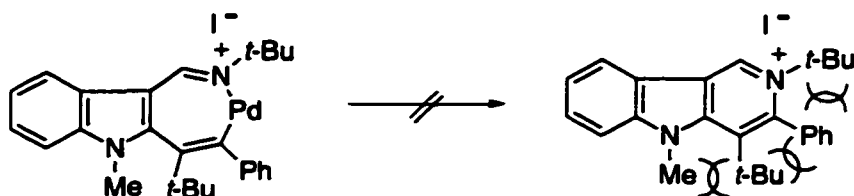
As mentioned earlier, the poor regioselectivity in our  $\beta$ -carboline synthesis can often be improved by simply adding one equiv TBAC (Table 2; entries 3, 5, and 9). Presumably, the chloride anion of the TBAC displaces the iodide in Pd(II) intermediate **A** and thus slows down the addition of intermediate **A** across the carbon-carbon triple bond of the alkyne, which was confirmed by the observation of prolonged reaction times (compare entries 2, 4, 8 and 13 with entries 3, 5, 9 and 14). Consequently, the reaction gives the more thermodynamically stable regioisomer as the major product.

It is now easy to understand why the annulation reaction of 3,3-dimethyl-1-phenyl-1-butyne by imine **3** produces only one isomer **22**. As previously mentioned, unsymmetrical alkynes usually give two regioisomers. However, in this case, this hindered alkyne is apparently unable to form the other regioisomer. To generate the other isomer, the corresponding vinylic Pd(II) intermediate has to undergo reductive elimination to generate a  $\beta$ -carbolinium salt having bulky *tert*-butyl groups in both the 2- and 3-positions. Apparently, the steric hindrance between these two *tert*-butyl groups disfavors formation of the anticipated  $\beta$ -carbolinium salt (see Figure 1).



**Figure 1.** Formation of the  $\beta$ -carbolinium salt is disfavored due to steric hindrance.

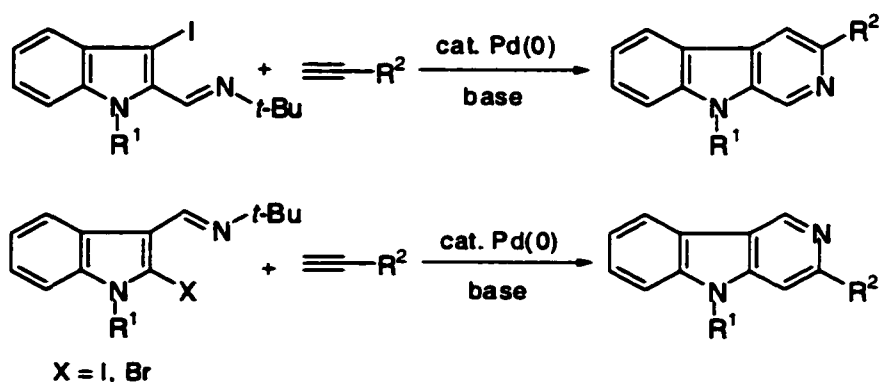
It is also understandable why the reaction of 3,3-dimethyl-1-phenyl-1-butyne and imine **43** didn't afford any  $\gamma$ -carboline product. Very likely, the steric hindrance between the 2-*tert*-butyl, 3-phenyl, 4-*tert*-butyl and the 5-methyl groups prevents formation of the anticipated  $\gamma$ -carbolinium intermediate (see Figure 2).



**Figure 2.** Formation of the  $\gamma$ -carbolinium salt is disfavored due to steric hindrance.

Thus far, our iminoannulation chemistry for the synthesis of  $\beta$ - and  $\gamma$ -carbolines has employed only internal alkynes. Although the palladium-catalyzed annulation of terminal alkynes has been rarely investigated,<sup>23</sup> we were determined to examine the palladium-catalyzed iminoannulation of terminal alkynes (Scheme 2) in order to broaden the scope and reduce the limitations of our iminoannulation chemistry. Previously, we have reported useful two-step approaches to the synthesis of  $\beta$ - and  $\gamma$ -carbolines involving the Sonogashira cross-coupling of terminal alkynes with the corresponding haloindolecarboxaldehydes, followed by imine formation with  $t$ -BuNH<sub>2</sub> and either CuI-catalyzed or thermal cyclization (Scheme 3).<sup>4j,k</sup> We hoped to be able to develop this approach into a more convenient one-step process. The results of this investigation are summarized in Table 4.

### Scheme 2



**Table 4. Synthesis of  $\beta$ - and  $\gamma$ -Carbolines by the Palladium-Catalyzed Annulation of Terminal Alkynes<sup>a</sup>**

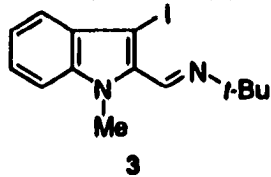
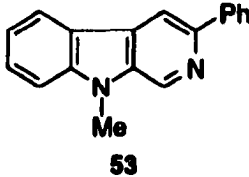
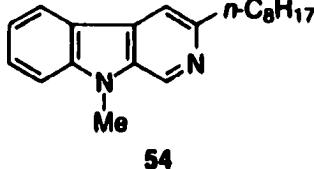
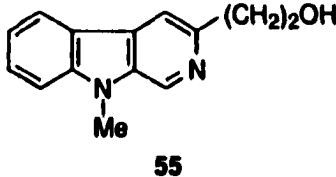
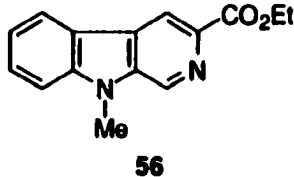
entry	imine	alkyne	cond.	time (h)	product	% isolated yield
1	 <b>3</b>	$\equiv$ -Ph	A	24	 <b>53</b>	43
2			A	24		33 <sup>b</sup>
3			C	5		34
4		$\equiv$ - <i>n</i> -C <sub>8</sub> H <sub>17</sub>	A	6	 <b>54</b>	32
5		$\equiv$ -(CH <sub>2</sub> ) <sub>2</sub> OH	A	7	 <b>55</b>	60
6		$\equiv$ -CO <sub>2</sub> Et	A	7	 <b>56</b>	trace

Table 4. Continued

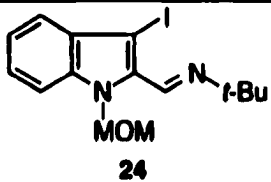
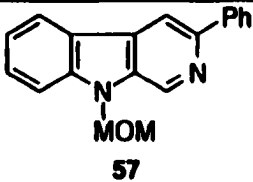
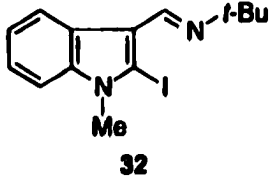
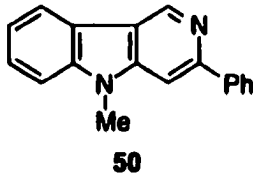
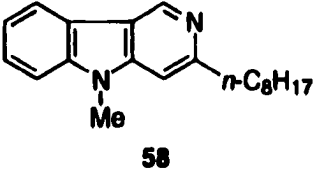
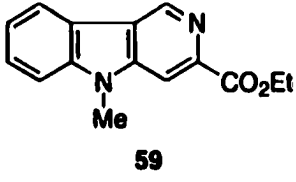
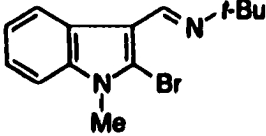
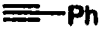
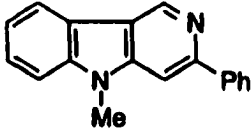

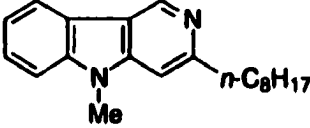
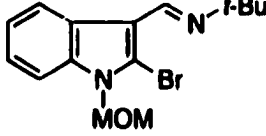

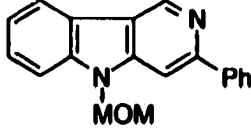
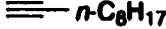
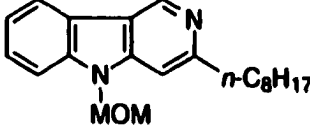
entry	imine	alkyne	cond.	time (h)	product	% isolated yield
7	 24	$\equiv$ -Ph	A	8	 57	44
8	 32	$\equiv$ -Ph	C	24	 50	56 <sup>c</sup>
9		$\equiv$ - <i>n</i> -C <sub>8</sub> H <sub>17</sub>	C	20	 58	42
10		$\equiv$ -CO <sub>2</sub> Et	C	20	 59	71

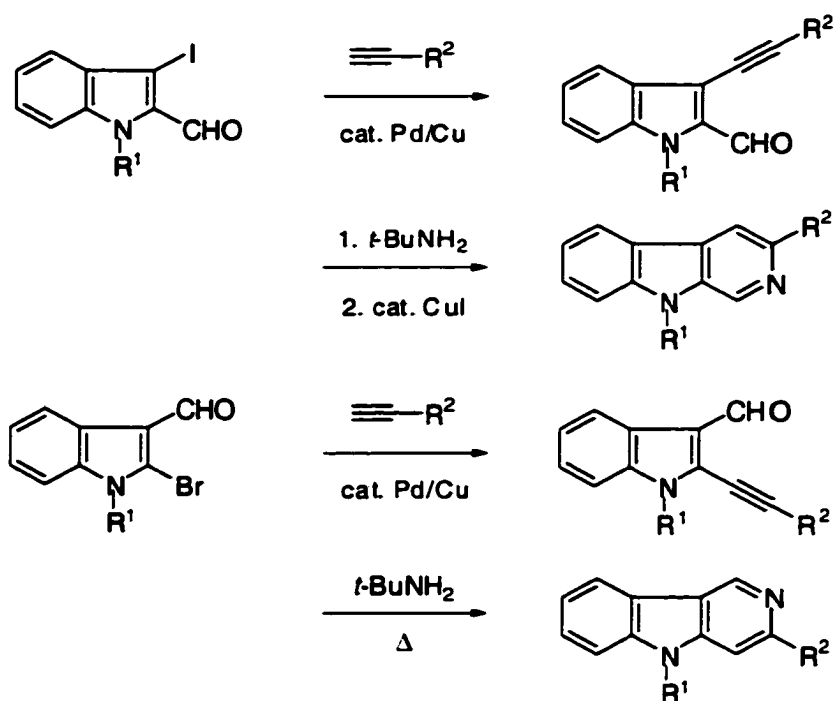
Table 4. Continued

entry	imine	alkyne	cond.	time (h)	product	% isolated yield
11	 <b>43</b>	 $\equiv$ -Ph	C <sup>d</sup>	24	 <b>50</b>	70
12		 $\equiv$ -n-C <sub>8</sub> H <sub>17</sub>	C <sup>d</sup>	18	 <b>58</b>	64
13	 <b>52</b>	 $\equiv$ -Ph	C <sup>d</sup>	24	 <b>60</b>	83
14		 $\equiv$ -n-C <sub>8</sub> H <sub>17</sub>	C <sup>d</sup>	16	 <b>61</b>	92

<sup>a</sup> Representative procedure for Conditions A: 5 mol % Pd(OAc)<sub>2</sub>, 5 mol % PPh<sub>3</sub>, *n*-Bu<sub>3</sub>N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: Na<sub>2</sub>CO<sub>3</sub> (0.25 mmol) was used as the base. <sup>b</sup> CuI (2 mol %) was added. <sup>c</sup> An inseparable mixture of carboline **50** and an unidentified by-product was isolated. The yield was based on <sup>1</sup>H NMR spectroscopy. <sup>d</sup> The reaction was run at 125 °C.



Scheme 3

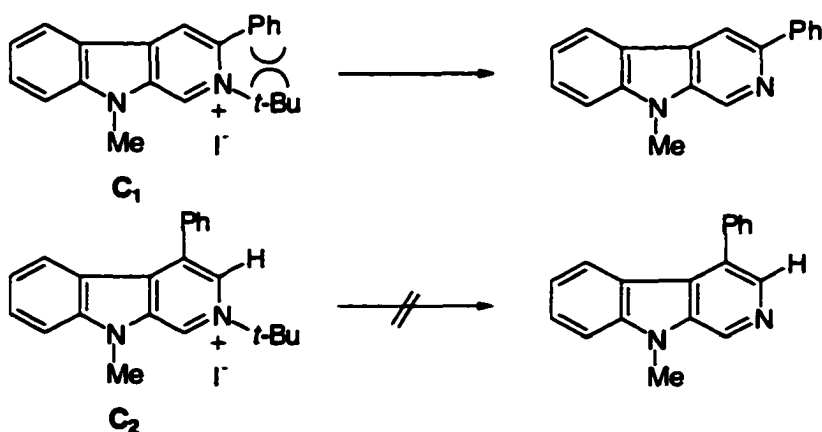


The annulation of imine **3** by phenylacetylene under our standard conditions for the synthesis of  $\beta$ -carbolines (Conditions A) was first examined. We were excited to see that only one regioisomer **53** was isolated, although in only a moderate 43% yield (Table 4, entry 1). Unfortunately, either adding 2 mol % of CuI to Conditions A or employing our standard conditions for the synthesis of  $\gamma$ -carbolines (Conditions C) afforded even lower yields of  $\beta$ -carboline **53** (entries 2 and 3). The reactions of 1-octyne and ethyl propiolate generated a low yield (32%) of  $\beta$ -carboline **54** and only a trace amount of the desired  $\beta$ -carboline **56**, respectively (entries 4 and 6). However, 3-butyn-1-ol afforded an appreciable 60% yield of the desired  $\beta$ -carboline **55** (entry 5). The annulation of phenylacetylene by the *N*-methoxymethyl protected imine **24** produced  $\beta$ -carboline **57** in a yield comparable to that of the methyl imine **3** (entry 7).

According to the mechanism we have proposed (Scheme 1), the annulation of imine **3** with a terminal acetylene, for example phenylacetylene, should generate two

isomeric *tert*-butylcarbolinium intermediate **C**<sub>1</sub> and **C**<sub>2</sub> (Scheme 4). As mentioned previously, the *tert*-butyl group of the *tert*-butylcarbolinium salt **C**<sub>1</sub> apparently fragments to relieve the strain resulting from interaction with the phenyl group present in the 3-position. However, the *tert*-butyl group of salt **C**<sub>2</sub> fails to fragment due to the lack of steric interaction between the *tert*-butyl group and the neighboring small hydrogen. Indeed, we have observed extremely polar and highly fluorescent compounds by TLC analysis in essentially every reaction mixture of the annulation of terminal alkynes by 3-iodoimines. These compounds were easily transferred into the aqueous layer during aqueous work-up. The evidence obtained from <sup>1</sup>H NMR spectra of the reaction mixture of imine **3** and phenylacetylene, and the contents in the aqueous layer after work-up also prove the existence of the corresponding *tert*-butylcarbolinium salt **C**<sub>2</sub>. That's probably why most of the reactions of 3-iodoimines with terminal alkynes only produce moderate yields of carboline. Moreover, terminal alkynes can undergo palladium-catalyzed homocoupling,<sup>24</sup> which might also decrease the yields of the annulation products.

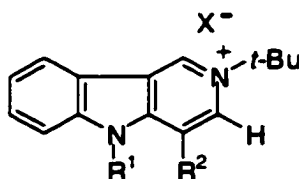
Scheme 4



The annulation of two terminal alkynes, namely phenylacetylene and 1-octyne, by 2-iodoimine **32** only produced moderate yields of the  $\gamma$ -carboline products **50** and **58** under our standard  $\gamma$ -carboline conditions (Conditions C) (entries 8 and 9). Interestingly, ethyl propiolate afforded a 71% yield of the desired  $\gamma$ -carboline **59**

(entry 10). The relatively low yields might be a direct result of the 2-iodoimine **32** being reduced during the reaction, which has been observed in other reactions employing internal alkynes.

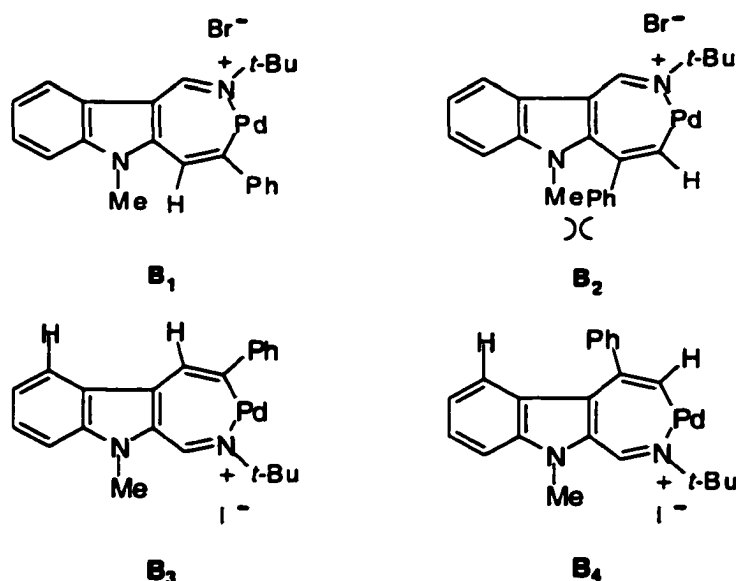
Surprisingly, when 2-bromoimine **43** was employed in the annulation reactions with phenylacetylene and 1-octyne at 125 °C, both reactions afforded reasonably good yields of the desired  $\gamma$ -carbolines **50** and **58** (entries 11 and 12). To our delight, the annulation of phenylacetylene and 1-decyne by *N*-methoxymethyl-substituted bromoimine **52** generated an 83% yield of  $\gamma$ -carboline **60** and a 92% yield of  $\gamma$ -carboline **61**, respectively. It is worth mentioning that we did not observe significant amounts of extremely polar and highly fluorescent compounds presumably corresponding to the isomeric *tert*-butylcarbolinium intermediates **C** (Figure 3) in the reactions employing 2-haloimines and terminal alkynes.



**Figure 3.** The isomeric *tert*-butyl- $\gamma$ -carbolinium salts **C** were not observed.

As seen from the mechanism we have proposed (Scheme 1), the annulation of imine **43** and phenylacetylene should, for example, form two isomeric 7-membered palladacyclic immonium salts **B<sub>1</sub>** and **B<sub>2</sub>** as intermediates (Figure 4). However, salt **B<sub>2</sub>** is more difficult to form due to steric interactions between the 4-phenyl and 5-methyl groups. Therefore, the energy difference between these two isomeric salts should be significant enough to result in the production of only one  $\gamma$ -carboline regioisomer. However, in the case of the annulation of imine **3** and phenylacetylene, because of the lack of steric interactions between the 4- and 5-positions, the energy difference between the two isomeric 7-membered palladacyclic immonium salts **B<sub>3</sub>** and **B<sub>4</sub>** should not be significant (Figure 4). Therefore, we are able to observe the *tert*-butyl- $\beta$ -carbolinium salt **C<sub>2</sub>** which arises from the reductive

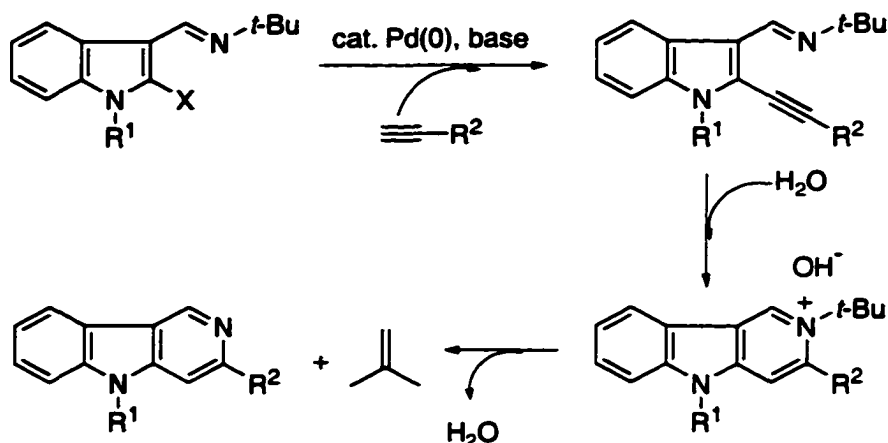
elimination of Pd(0) from immonium salt **B**<sub>4</sub> by TLC and NMR analysis, as mentioned earlier.



**Figure 4.** Salts **B**<sub>1</sub> and **B**<sub>2</sub> should have significantly different energy, but **B**<sub>3</sub> and **B**<sub>4</sub> should not.

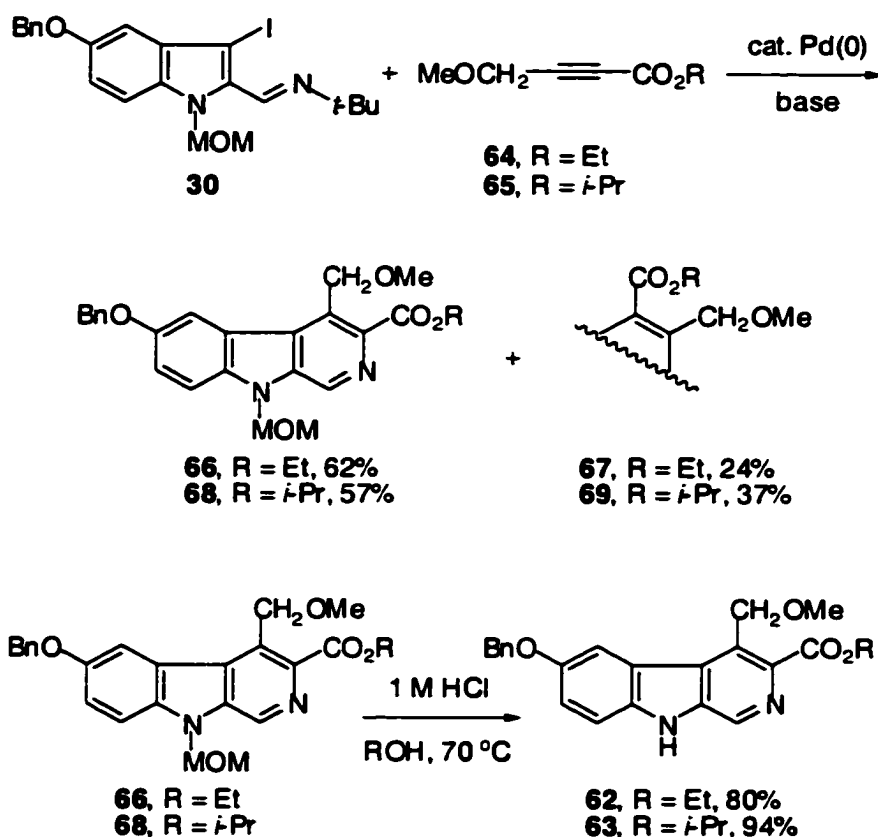
Alternatively, since only the 3-substituted  $\gamma$ -carboline product was observed, other mechanisms might be operating in this system. The following alternative mechanism may be envisioned for this transformation (Scheme 5). Specifically, the Sonogashira coupling of 2-haloindole imine with a terminal alkyne produces an intermediate 2-(1-alkynyl)indole imine, which can then be cyclized thermally in the presence of spurious amount of water, producing a *tert*-butylcarbolinium salt, which apparently fragments, producing the  $\gamma$ -carboline.<sup>4k</sup> Although we have been unable to observe the 2-(1-alkynyl)indole imine intermediate when the reaction of imine **52** and phenylacetylene was stopped after only 1 h, the mechanism proposed in Scheme 5 is still possible for this process and cannot be excluded.

Scheme 5



To demonstrate the versatility of this annulation chemistry, we have applied the palladium-catalyzed iminoannulation process to the synthesis of two biologically interesting  $\beta$ -carboline alkaloids ZK93423 (**62**) and abecarnil (ZK112119, **63**). ZK93423 is a full agonist at the wild type and recombinant GABA<sub>A</sub> receptor,<sup>18</sup> and abecarnil displays metabolically stable, anxiolytic activity at benzodiazapine receptors and anticonvulsant properties.<sup>19</sup> Although the syntheses of ZK93423<sup>18b,d</sup> and abecarnil<sup>19c</sup> have been achieved previously, our approach may provide a useful alternative to existing methodology. Upon examination of the structures of ZK93423 and abecarnil, we felt that they could be synthesized by employing our palladium-catalyzed iminoannulation using 1-methoxymethyl-5-benzyloxy-substituted imine **30** and internal alkynes **64** and **65**, followed by acid-promoted deprotection of the *N*-methoxymethyl group (Scheme 6). Despite our concern that the annulation reactions might produce two regioisomers, we anticipated that the desired isomer would be the major one required for the synthesis of ZK93423 (**62**) and abecarnil (**63**).

## Scheme 6



By employing the standard reaction conditions for our  $\beta$ -carboline synthesis (Conditions A), the annulation of ethyl 4-methoxy-2-butynoate (**64**) by imine **30** fortunately produced the desired  $\beta$ -carboline **66** in a 62% yield, along with a 24% yield of regioisomer **67**. It is noteworthy that when employing Conditions B, which contains one equiv of *n*-Bu<sub>4</sub>NCl (TBAC), the same reaction generated a similar combined yield, but with decreased regioselectivity, presumably due to coordination of the 4-methoxy group to the palladium. Similarly, the annulation of isopropyl 4-methoxy-2-butynoate (**65**) by imine **30** under Conditions A afforded a 57% yield of the desired isomer **68**, as well as a 37% yield of regioisomer **69**. To avoid hydrolysis of the ethyl and isopropyl esters in the 3-position during acid-promoted deprotection of the *N*-methoxymethyl group, EtOH and *i*-PrOH were chosen as the solvents for deprotection of the  $\beta$ -carbolines **66** and **68**, respectively. The acid-promoted

deprotection proceeded smoothly at 70 °C, generating ZK93423 (**62**) in an 80% yield and abecarnil (**63**) in a 94% yield, respectively (Scheme 6).

### Conclusions

An efficient, palladium-catalyzed synthesis of substituted  $\beta$ - and  $\gamma$ -carbolines from simple internal and terminal alkynes and the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes has been developed. The best reaction conditions for the  $\beta$ -carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of Pd(OAc)<sub>2</sub>, 5 mol % of PPh<sub>3</sub> and 1 equiv of *n*-Bu<sub>3</sub>N as the base in 5 mL of DMF at 100 °C. The preferred conditions for the  $\gamma$ -carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of Pd(OAc)<sub>2</sub>, 10 mol % of PPh<sub>3</sub> and 1 equiv of Na<sub>2</sub>CO<sub>3</sub> as the base in 5 mL of DMF at 100 or 125 °C. A wide variety of aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl- and trimethylsilyl-substituted acetylenes undergo this process in moderate to excellent yields. When unsymmetrical internal alkynes are employed, mixtures of regioisomers are observed in most cases. When terminal alkynes are employed, only one regioisomer has been isolated. This annulation chemistry has also been successfully applied to the synthesis of two biologically interesting  $\beta$ -carboline alkaloids, ZK93423 and abecarnil (ZK112119).

### Experimental Section

**General.** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. 3-Iodo-1-methylindole-2-carboxaldehyde, 2-bromo-1-methylindole-3-carboxaldehyde, 2-bromo-1-methoxymethylindole-3-carboxaldehyde and compounds **1-6**, **11**, **16**, **24**, **25**, **32-35**, **39**, **43**, **44**, **46**, **50**, **52**, **53-55**, **57**, **58** and **60** have been previously

reported.<sup>4k,17</sup> 3-Iodo-1*H*-indole-2-carboxaldehyde,<sup>25</sup> 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,<sup>25</sup> and 2-bromo-1*H*-indole-3-carboxaldehyde<sup>26</sup> were prepared according to previous literature procedures. Following are the preparation and characterization of the starting materials 1-benzyl-3-iodoindole-2-carboxaldehyde, 3-iodo-1-tosylindole-2-carboxaldehyde, 5-benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxaldehyde, 2-iodo-1-(methoxymethyl)indole-3-carboxaldehyde, ethyl 4-methoxy-2-butynoate (**64**) and isopropyl 4-methoxy-2-butynoate (**65**).

**1-Benzyl-3-iodoindole-2-carboxaldehyde.** This aldehyde was prepared as a white solid in 100% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,<sup>25</sup> only employing 3-iodo-1*H*-indole-2-carboxaldehyde and benzyl iodide: mp 114-115 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.84 (s, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.20-7.27 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.43 (dt, *J* = 8.0, 0.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 10.00 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 48.0, 111.4, 122.1, 123.9, 126.6, 127.6, 128.5, 128.7, 130.0, 131.1, 137.4, 140.4, 184.5.

**3-Iodo-1-tosylindole-2-carboxaldehyde.** This aldehyde was prepared as a yellow solid in 73% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,<sup>25</sup> only employing 3-iodo-1*H*-indole-2-carboxaldehyde and tosyl chloride: mp 155-156 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.34 (s, 3H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.39 (m, 1H), 7.53-7.60 (m, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 8.4 Hz, 1H), 10.42 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.9, 81.7, 115.8, 125.0, 125.6, 127.1, 130.1, 130.2, 132.5, 134.5, 134.7, 137.9, 146.1, 183.3.

**5-Benzyloxy-3-iodo-1*H*-indole-2-carboxaldehyde.** This aldehyde was prepared as a yellow solid in an overall 38% yield by the reaction sequence used to prepare 3-iodo-1*H*-indole-2-carboxaldehyde,<sup>25</sup> only starting with ethyl 5-benzyloxy-1*H*-indole-2-carboxylate:<sup>27</sup> mp 160-162 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 5.19 (s, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 9.80 (s, 1H); <sup>13</sup>C



NMR (acetone- $d_6$ )  $\delta$  70.2, 103.6, 114.5, 114.6, 120.4, 127.7, 127.8, 128.4, 130.9, 133.3, 134.2, 137.5, 154.9, 182.1.

**5-Benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde.** This aldehyde was prepared as a yellow solid in 83% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,<sup>25</sup> only employing 5-benzyloxy-3-iodo-1*H*-indole-2-carboxaldehyde and methoxymethyl chloride: mp 110-112 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.28 (s, 3H), 5.15 (s, 2H), 5.94 (s, 2H), 7.03 (d,  $J$  = 2.4 Hz, 1H), 7.23 (dd,  $J$  = 9.0, 2.4 Hz, 1H), 7.35-7.52 (m, 6H), 9.98 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  56.3, 70.9, 74.9, 78.1, 104.7, 113.2, 121.5, 128.0, 128.4, 128.9, 130.9, 131.9, 136.0, 136.9, 155.5, 184.5.

**2-Iodo-1*H*-indole-3-carboxaldehyde.** POCl<sub>3</sub> (0.9 mL, 9.6 mmol) was added slowly by a syringe to ice-cooled dry DMF (10 mL). The solution, protected from moisture with a drying tube, was stirred for 15 min at room temperature and then recooled to around 0 °C. A solution of 2-iodoindole<sup>28</sup> (2.13 g, 8.76 mmol) in DMF (10 mL) was then added over 5 min. The mixture was stirred at room temperature for 3 h and then poured into ice water (50 mL). The yellow mixture was made alkaline with NaOH (1.5 g) in water (10 mL). The mixture was quickly boiled for 1 min and extracted with ether. The organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum and the residue was chromatographed using 3:1 hexanes:EtOAc to afford a yellow solid (1.66 g, 70%): mp 218-219 °C (decomp); <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  7.24-7.32 (m, 2H), 7.45-7.48 (m, 1H), 8.17-8.19 (m, 1H), 10.11 (s, 1H), 11.75 (s, 1H); <sup>13</sup>C NMR (acetone- $d_6$ )  $\delta$  90.0, 112.3, 113.7, 121.4, 123.7, 124.9, 125.7, 135.8, 183.9.

**2-Iodo-1-(methoxymethyl)indole-3-carboxaldehyde.** This aldehyde was prepared as a yellow oil in 67% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,<sup>25</sup> only employing 2-iodo-1*H*-indole-3-carboxaldehyde and methoxymethyl chloride: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.30 (s, 3H), 5.50 (s, 2H), 7.27-7.34 (m, 2H), 7.38-7.45 (m, 1H), 8.21-8.28 (m, 1H), 10.10 (s, 1H); <sup>13</sup>C

NMR (CDCl<sub>3</sub>)  $\delta$  56.8, 74.4, 110.5, 114.0, 121.5, 124.1, 124.6, 124.8, 136.0, 136.5, 184.6.

**Ethyl 4-methoxy-2-butynoate (64).** A hexane solution of *n*-BuLi (2.5 M, 3.6 mL) was added to a THF (20 mL) solution of methyl propargyl ether (0.526 g, 7.5 mmol) at  $-78\text{ }^{\circ}\text{C}$  under Ar and the mixture was stirred for 30 min. Ethyl chloroformate (0.977 g, 1.2 equiv) in THF (10 mL) was added. After stirring at  $-78\text{ }^{\circ}\text{C}$  for 1 h, the reaction was quenched by satd. aq. NH<sub>4</sub>Cl and extracted by EtOAc. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was chromatographed using 7:1 hexanes/EtOAc to afford a colorless oil (0.876 g, 82%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.32 (t, *J* = 7.2 Hz, 3H), 3.42 (s, 3H), 4.24 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.0, 58.1, 59.4, 62.1, 78.2, 83.0, 153.1.

**Isopropyl 4-methoxy-2-butynoate (65).** This ester was prepared as a colorless oil in 52% yield by the method used to prepare ethyl 4-methoxy-2-butynoate (64), only employing methyl propargyl ether and isopropyl chloroformate: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.30 (d, *J* = 6.4 Hz, 6H), 3.42 (s, 3H), 4.23 (s, 2H), 5.10 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.6, 58.1, 59.4, 70.1, 78.6, 82.6, 152.7.

### Imines Prepared.

**1-Benzyl-3-iodoindole-2-methylene-*tert*-butylamine (26).** The imine was prepared by the method used to prepare **1**,<sup>17</sup> only employing 1-benzyl-3-iodoindole-2-carboxaldehyde (180 mg, 0.5 mmol). Removal of the solvent afforded 210 mg (100%) of the imine as a yellow viscous oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.22 (s, 9H), 6.06 (s, 2H), 7.05 (d, *J* = 6.8 Hz, 2H), 7.15-7.22 (m, 4H), 7.27-7.31 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 8.49 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  28.4, 47.0, 57.2, 67.4, 109.5, 119.8, 121.0, 124.0, 125.6, 125.8, 127.2, 129.0, 131.8, 137.6, 138.6, 147.7; IR (neat, cm<sup>-1</sup>) 3061, 2967; HRMS calcd for C<sub>20</sub>H<sub>21</sub>IN<sub>2</sub>: 416.0750. Found: 416.0757.

**3-Iodo-1-tosylindole-2-methylene-*tert*-butylamine (28).** This imine was prepared by the method used to prepare imine **1**,<sup>17</sup> only employing 3-iodo-1-tosylindole-2-carboxaldehyde (212 mg, 0.5 mmol). Removal of the solvent afforded

240 mg (100%) of the imine as a yellow viscous oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H), 2.30 (s, 3H), 7.15 (d,  $J = 8.0$  Hz, 2H), 7.31 (t,  $J = 7.6$  Hz, 1H), 7.37-7.43 (m, 2H), 7.60 (d,  $J = 8.0$  Hz, 2H), 8.10 (d,  $J = 8.0$  Hz, 1H), 8.59 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.6, 29.6, 59.2, 73.9, 114.8, 123.3, 124.6, 126.8, 126.9, 129.9, 132.8, 134.6, 135.7, 136.2, 145.3, 148.7; IR (neat,  $\text{cm}^{-1}$ ) 3022, 2964; HRMS calcd for  $\text{C}_{20}\text{H}_{21}\text{IN}_2\text{O}_2\text{S}$ : 480.0369. Found: 480.0375.

**5-Benzyloxy-3-iodo-1-(methoxymethyl)indole-2-methylene-*tert*-butylamine (30).** This imine was prepared by the method used to prepare imine 1,<sup>17</sup> only employing 5-benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde (463 mg, 1.1 mmol). Removal of the solvent afforded 524 mg (100%) of the imine as a yellow solid: mp 97-98 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.33 (s, 9H), 3.27 (s, 3H), 5.14 (s, 2H), 6.21 (s, 2H), 7.00 (d,  $J = 2.4$  Hz, 1H), 7.08 (dd,  $J = 9.0, 2.4$  Hz, 1H), 7.33-7.52 (m, 6H), 8.48 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.8, 55.8, 58.7, 70.3, 71.0, 74.7, 104.6, 112.5, 117.1, 128.0, 128.2, 128.8, 131.0, 133.9, 135.1, 137.4, 149.3, 154.9; IR (neat,  $\text{cm}^{-1}$ ) 3017, 2969, 2927; HRMS calcd for  $\text{C}_{22}\text{H}_{25}\text{IN}_2\text{O}_2$ : 476.0961. Found: 476.0971.

**2-Iodo-1-(methoxymethyl)indole-3-methylene-*tert*-butylamine (38).** This imine was prepared by the method used to prepare imine 1,<sup>17</sup> only employing 2-iodo-1-(methoxymethyl)indole-3-carboxaldehyde (157 mg, 0.5 mmol). Removal of the solvent afforded 185 mg (100%) of the imine as a pale yellow solid: mp 108-110 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.34 (s, 9H), 3.29 (s, 3H), 5.55 (s, 2H), 7.22-7.30 (m, 2H), 7.40-7.43 (m, 1H), 8.50-8.54 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.0, 56.1, 57.4, 73.9, 109.5, 112.0, 122.3, 122.4, 123.6, 125.4, 128.9, 136.2, 148.3; IR (neat,  $\text{cm}^{-1}$ ) 3054, 2964; HRMS calcd for  $\text{C}_{15}\text{H}_{19}\text{IN}_2\text{O}$ : 370.0542. Found: 370.0547.

**2-Iodo-1*H*-indole-3-methylene-*tert*-butylamine (40).** This imine was prepared by the method used to prepare imine 1,<sup>17</sup> only employing 2-iodo-1*H*-indole-3-carboxaldehyde (215 mg, 0.79 mmol) for 6 h. Removal of the solvent afforded 260 mg (100%) of the imine as a pale yellow solid: mp 155-157 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49 (s, 9H), 7.16-7.26 (m, 2H), 7.40 (d,  $J = 6.8$  Hz, 1H), 7.58 (d,  $J = 7.6$  Hz, 1H), 7.76 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.1, 54.7, 117.8 (broad), 119.6 (broad), 123.0,

124.3 (broad), 144.0 (broad). The  $^{13}\text{C}$  NMR spectrum of compound **40** gives incomplete (four  $\text{sp}^2$  carbons missing) and unusually broad peaks for the indole ring, even when the background noise is very low; IR (neat,  $\text{cm}^{-1}$ ) 3184, 3052, 2974, 1635; HRMS calcd for  $\text{C}_{13}\text{H}_{15}\text{IN}_2$ : 326.0280. Found: 326.0286.

**2-Bromo-1*H*-indole-3-methylene-*tert*-butylamine (42).** This imine was prepared by the method used to prepare imine **1**,<sup>17</sup> only employing 2-bromo-1-*H*-indole-3-carboxaldehyde (223 mg, 1.0 mmol) for 6 h. Removal of the solvent afforded 278 mg (100%) of the imine as a yellow solid: mp 152-153 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49, 7.15-7.26 (m, 2H), 7.44 (d,  $J = 6.9$  Hz, 1H), 7.58-7.61 (m, 1H), 7.75 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.3, 55.0, 117.6 (broad), 119.6, 123.2, 124.4, 145.3 (broad), 145.9 (broad). The  $^{13}\text{C}$  NMR spectrum of compound **42** gives incomplete (three  $\text{sp}^2$  carbons missing) and unusually broad peaks for the indole ring, even when the background noise is very low, which is very similar to compound **40**; IR (neat,  $\text{cm}^{-1}$ ) 3181, 3054, 2971, 1633; HRMS calcd for  $\text{C}_{13}\text{H}_{15}\text{BrN}_2$ : 278.0419. Found: 278.0423.

#### **General Procedure for the Palladium-Catalyzed Formation of Carbolines.**

Conditions A: DMF (5 mL),  $\text{Pd}(\text{OAc})_2$  (3.0 mg, 0.013 mmol),  $\text{PPh}_3$  (3.3 mg, 0.013 mmol), *n*- $\text{Bu}_3\text{N}$  (47 mg, 0.25 mmol), and the alkyne (0.5 mmol) [Conditions B: *n*- $\text{Bu}_4\text{NCl}$  (TBAC, 46 mg, 0.25 mmol), everything else is the same as in Conditions A. Conditions C:  $\text{PPh}_3$  (6.5 mg, 0.025 mmol),  $\text{Na}_2\text{CO}_3$  instead of *n*- $\text{Bu}_3\text{N}$  (26.5 mg, 0.25 mmol), everything else is the same as in Conditions A] were placed in a 4 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.25 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 100 or 125 °C for the indicated period of time. The completion of the reactions was established by the observation of palladium black. The reaction mixture (except entries 10 and 11 in Table 2 and entry 16 in Table 3, which afford fairly water soluble carbolines) was cooled, diluted with ether, washed with satd aq  $\text{NH}_4\text{Cl}$ , dried ( $\text{Na}_2\text{SO}_4$ ), and filtered. The solvent was evaporated under reduced pressure and the product was isolated

by chromatography on a silica gel column. The reaction mixtures of entries 10 and 11 in Table 1 and entry 16 in Table 3 were filtered, the solvent was removed directly under reduced pressure, and the residue was purified by chromatography.

### Carbolines Prepared

**4,9-Dimethyl-3-phenyl-9H-pyrido[3,4-*b*]indole (7).** The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 34 mg (49%) of the indicated compound as a white solid: mp 179-180 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 2.89 (s, 3H), 4.06 (s, 3H), 7.30-7.42 (m, 2H), 7.45-7.51 (m, 2H), 7.60-7.71 (m, 4H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.92 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 17.8, 110.4, 120.4, 122.8, 124.7, 124.9, 127.7, 128.3, 128.4, 128.6, 130.3, 131.0, 136.9, 142.6, 143.0, 149.3 (one sp<sup>3</sup> carbon missing due to overlap); IR (neat, cm<sup>-1</sup>) 3058, 2924; HRMS calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>: 272.1314. Found: 272.1318.

**3,9-Dimethyl-4-phenyl-9H-pyrido[3,4-*b*]indole (8).** The reaction mixture was chromatographed using EtOAc to afford 29 mg (42%) of the indicated compound as a white solid: mp 117-119 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 2.42 (s, 3H), 4.02 (s, 3H), 6.85-6.95 (m, 2H), 7.40-7.85 (m, 7H), 8.89 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 22.3, 29.5, 110.2, 119.7, 121.7, 123.7, 127.7, 128.5, 128.6, 129.5, 129.9, 130.0, 131.2, 132.7, 139.9, 143.1, 145.2; IR (neat, cm<sup>-1</sup>) 3053, 2924; HRMS calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>: 272.1314. Found: 272.1318. The regiochemistry of carbolines **7** and **8** was determined by comparison of the spectral data for these compounds with those of carboline **4**.<sup>17</sup> Compared to the chemical shift of 5-H in carboline **7**, the chemical shift of 5-H in carboline **8** is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline **8**.

**4-Hydroxymethyl-9-methyl-3-phenyl-9H-pyrido[3,4-*b*]indole (9).** The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 26 mg (36%) of the indicated compound as a white solid: mp 193-195 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.98 (s, 3H), 4.93 (s, 1H), 5.40 (s, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.35-7.47 (m, 3H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 3H), 8.41 (d, *J* = 7.6 Hz, 1H), 9.02

(s, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  29.8, 59.4, 110.3, 120.0, 120.9, 125.4, 126.7, 127.7, 128.2, 128.3, 128.4, 130.4, 132.0, 136.5, 141.1, 142.3, 148.2; IR (neat,  $\text{cm}^{-1}$ ) 3214, 3056, 2925; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ : 288.1263. Found: 288.1268.

**3-Hydroxymethyl-9-methyl-4-phenyl-9H-pyrido[3,4-*b*]indole (10).** The reaction mixture was chromatographed using 1:1 EtOAc/acetone to afford 31 mg (43%) of the indicated compound as a white solid: mp 278-280 °C;  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  4.08 (s, 3H), 4.44 (s, 1H), 4.53 (s, 2H), 6.95-7.01 (m, 2H), 7.47-7.50 (m, 2H), 7.52-7.56 (m, 1H), 7.59-7.66 (m, 4H), 9.01 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  62.5, 110.4, 120.1, 121.8, 124.0, 128.3, 129.0, 129.1, 129.2, 129.9, 130.1, 130.6, 137.8, 143.7, 146.6 (one  $\text{sp}^3$  and one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3195, 3056, 2922; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ : 288.1263. Found: 288.1268. The regiochemistry of carboline 9 and 10 was determined by comparison of the spectral data for these compounds with those of carboline 4.<sup>17</sup> Compared to the chemical shift of 5-H in carboline 9, the chemical shift of 5-H in carboline 10 is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline 10.

**Ethyl 3,9-dimethyl-9H-pyrido[3,4-*b*]indole-4-carboxylate (12) and ethyl 4,9-dimethyl-9H-pyrido[3,4-*b*]indole-3-carboxylate (13).** The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 49 mg (73%) of the indicated compounds as a yellow solid (1:1 inseparable mixture of isomers).  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  1.41 (t,  $J = 7.2$  Hz, 3H), 1.46 (t,  $J = 7.2$  Hz, 3H), 2.68 (s, 3H), 3.03 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 4.40 (q,  $J = 7.2$  Hz, 2H), 4.61 (q,  $J = 7.2$  Hz, 2H), 7.25 (m, 1H), 7.35 (m, 1H), 7.65 (m, 4H), 8.09 (d,  $J = 8.1$  Hz, 1H), 8.35 (d,  $J = 8.1$  Hz, 1H), 8.86 (s, 1H), 8.96 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  14.5, 14.7, 16.5, 22.6, 29.7, 61.3, 62.2, 110.6, 110.8, 120.1, 120.4, 121.0, 121.2, 122.6, 124.1, 124.7, 125.9, 127.7, 128.7, 129.5, 130.1, 132.7, 133.6, 136.3, 138.0, 142.9, 143.3, 144.7, 168.3, 169.4; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2927, 1717; HRMS calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ : 268.1212. Found: 268.1217.

**4-Hydroxymethyl-3,9-dimethyl-9H-pyrido[3,4-*b*]indole (14) and 3-hydroxymethyl-4,9-dimethyl-9H-pyrido[3,4-*b*]indole (15).** The reaction mixture was chromatographed using acetone to afford 68 mg (100%) of a 1:1 inseparable mixture of the indicated compounds as an off-white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.70 (s, 3H), 2.82 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 4.79 (s, 2H), 5.04 (s, 2H), 5.05 (s, 1H), 5.23 (s, 1H), 7.23-7.31 (m, 2H), 7.55-7.70 (m, 4H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.78 (s, 1H), 8.81 (s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 15.3, 21.7, 29.6, 29.7, 58.4, 63.8, 110.1, 110.3, 119.6, 119.9, 120.6, 121.5, 124.1, 125.1, 125.5, 127.3, 127.5, 128.1, 128.2, 128.6, 130.9, 136.4, 136.6, 142.1, 142.2, 145.5, 147.6; IR (neat, cm<sup>-1</sup>) 3350, 3012, 2924; HRMS calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: 226.1106. Found: 226.1111.

**Diethyl 9-methyl-9H-pyrido[3,4-*b*]indole-3,4-dicarboxylate (17).** The reaction was carried out under conditions A (Table 2, entry 12) and the mixture was chromatographed using 1:4 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a white solid: mp 154-155 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 1.41 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 4.13 (s, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.59 (q, *J* = 7.2 Hz, 3H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.69-7.77 (m, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 9.12 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 14.7, 15.0, 62.3, 62.9, 111.6, 120.7, 121.9, 124.1, 125.4, 126.0, 130.5, 133.6, 136.4, 139.0, 143.7, 166.8, 168.5; IR (neat, cm<sup>-1</sup>) 2987, 1734, 1718; HRMS calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: 326.1267. Found: 326.1273.

**9-Methyl-3-phenyl-4-trimethylsilyl-9H-pyrido[3,4-*b*]indole (18).** The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford 28 mg (34%) of the indicated compound as a yellow solid: mp 138-140 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 0.21 (s, 9H), 4.06 (s, 3H), 7.31 (m, 1H), 7.40-7.49 (m, 3H), 7.55-7.70 (m, 4H), 8.32 (dd, *J* = 8.1, 0.9 Hz, 1H), 9.01 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 1.0, 28.8, 110.0, 118.9, 121.9, 124.6, 125.8, 127.6, 127.87, 127.9, 130.7, 132.2, 134.0, 135.3, 142.6, 146.1, 156.3; IR (neat, cm<sup>-1</sup>) 3057, 2932; HRMS calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>Si: 330.1552. Found: 330.1557.

**9-Methyl-4-phenyl-3-trimethylsilyl-9H-pyrido[3,4-*b*]indole (19).** The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 21 mg (25%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  0.04 (s, 9H), 4.05 (s, 3H), 6.83 (d,  $J = 7.8$  Hz, 1H), 6.94 (dt,  $J = 7.8, 0.9$  Hz, 1H), 7.42-7.46 (m, 2H), 7.51 (dd,  $J = 7.2, 1.2$  Hz, 1H), 7.58-7.63 (m, 4H), 9.17 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  -0.04, 28.9, 109.6, 119.4, 121.2, 123.1, 125.2, 127.8, 128.2, 128.6, 130.1, 132.1, 136.3, 138.2, 139.9, 141.8, 151.5; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2953; HRMS calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{Si}$ : 330.1552. Found: 330.1557. The regiochemistry of carbolines **18** and **19** was determined by comparison of the spectral data for these compounds with those of carboline **4**.<sup>17</sup> Compared to the chemical shift of 5-H in carboline **18**, the chemical shift of 5-H in carboline **19** is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline **19**.

**3,9-Dimethyl-4-trimethylsilyl-9H-pyrido[3,4-*b*]indole (20).** The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 21 mg (31%) of the indicated compound as a yellow solid: mp 186-187 °C;  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  0.61 (s, 9H), 2.80 (s, 3H), 3.99 (s, 3H), 7.22-7.28 (m, 1H), 7.56-7.64 (m, 2H), 8.27 (d,  $J = 8.4$  Hz, 1H), 8.87 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  1.9, 27.4, 28.6, 109.7, 118.5, 121.3, 124.0, 126.2, 127.6, 132.3, 133.1, 135.1, 142.5, 151.6; IR (neat,  $\text{cm}^{-1}$ ) 3027, 2922; HRMS calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{Si}$ : 268.1396. Found: 268.1400.

**4,9-Dimethyl-3-trimethylsilyl-9H-pyrido[3,4-*b*]indole (21).** The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 15 mg (22%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  0.43 (s, 9H), 2.97 (s, 3H), 3.99 (s, 3H), 7.28-7.32 (m, 1H), 7.58-7.65 (m, 2H), 8.27 (d,  $J = 8.0$  Hz, 1H), 8.99 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  -0.2, 17.8, 109.4, 119.5, 121.7, 123.7, 125.4, 127.3, 130.5, 133.3, 136.5, 141.4, 151.8 (one  $\text{sp}^3$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3030, 2924; HRMS calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{Si}$ : 268.1396. Found: 268.1400. The regiochemistry of carboline **21** was determined from its NOESY spectrum.

**4-*tert*-Butyl-9-methyl-3-phenyl-9H-pyrido[3,4-*b*]indole (22).** The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 25 mg (32%) of



the indicated compound as a yellow solid: mp 152-154 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.55 (s, 9H), 3.99 (s, 3H), 7.33-7.42 (m, 6H), 7.54 (d,  $J = 8.0$  Hz, 1H), 7.63 (t,  $J = 7.6$  Hz, 1H), 8.48 (d,  $J = 8.4$  Hz, 1H), 8.82 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.4, 32.6, 36.1, 109.3, 119.0, 121.2, 126.9, 127.2, 127.6, 127.7, 128.5, 128.9, 129.8, 136.6, 137.8, 142.1, 146.2, 148.4. The regiochemistry of carboline **22** was determined from its NOESY spectrum. IR (neat,  $\text{cm}^{-1}$ ) 3010, 2926; HRMS calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2$ : 314.1783. Found: 314.1787.

**9-Benzyl-3,4-diphenyl-9H-pyrido[3,4-*b*]indole (27).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 103 mg (100%) of the indicated compound as a yellow solid: mp 200-201 °C;  $^1\text{H}$  NMR (acetone- $\text{d}_6$ )  $\delta$  5.86 (s, 2H), 6.95-7.05 (m, 2H), 7.16 (m, 3H), 7.25-7.35 (m, 5H), 7.40 (m, 4H), 7.45-7.55 (m, 4H), 7.71 (d,  $J = 8.4$  Hz, 1H), 9.12 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $\text{d}_6$ )  $\delta$  46.3, 110.1, 119.5, 121.5, 123.3, 126.4, 126.9, 127.2, 127.5, 127.6, 127.7, 128.1, 128.7, 128.8, 129.4, 130.3, 130.4, 131.5, 135.8, 137.5, 138.7, 141.4, 142.0, 147.1; IR (neat,  $\text{cm}^{-1}$ ) 3057, 2922; HRMS calcd for  $\text{C}_{30}\text{H}_{22}\text{N}_2$ : 410.1783. Found: 410.1787.

**3,4-Diphenyl-9-tosyl-9H-pyrido[3,4-*b*]indole (29).** The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford 37 mg (32%) of the indicated compound as a white solid: mp 238-239 °C;  $^1\text{H}$  NMR (acetone- $\text{d}_6$ )  $\delta$  2.35 (s, 3H), 6.77 (d,  $J = 7.8$  Hz, 1H), 7.16 (t,  $J = 8.4$  Hz, 1H), 7.19-7.23 (m, 3H), 7.30-7.35 (m, 2H), 7.35-7.43 (m, 4H), 7.43-7.50 (m, 3H), 7.64 (m, 1H), 7.98 (d,  $J = 8.4$  Hz, 2H), 8.43 (d,  $J = 8.7$  Hz, 1H), 9.70 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $\text{d}_6$ )  $\delta$  21.5, 115.6, 124.4, 124.9, 125.4, 127.7, 128.0, 128.2, 129.0, 129.8, 130.5, 130.6, 130.9, 131.0, 131.2, 132.2, 134.4, 135.4, 136.2, 138.0, 140.0, 141.1, 147.2, 152.7; IR (neat,  $\text{cm}^{-1}$ ) 3061, 2923; HRMS calcd for  $\text{C}_{30}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ : 474.1402. Found: 474.1409.

**6-Benzyloxy-9-methoxymethyl-3,4-diphenyl-9H-pyrido[3,4-*b*]indole (31).** The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 92 mg (79%) of the indicated compound as a white solid: mp 163-164 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.37 (s, 3H), 4.75 (s, 2H), 5.77 (s, 2H), 6.57 (d,  $J = 2.4$  Hz, 1H), 7.15-7.41 (m, 16H), 7.50 (d,  $J = 8.8$  Hz, 1H), 9.07 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  56.5, 70.2, 74.6,

106.8, 110.7, 119.2, 122.4, 126.7, 127.6 (2), 127.7, 127.9, 128.3, 128.5, 128.6, 129.7, 130.2, 130.4, 131.3, 136.3, 136.9, 137.0, 138.0, 140.7, 147.8, 153.1; IR (neat,  $\text{cm}^{-1}$ ) 3040, 2976, 2871; HRMS calcd for  $\text{C}_{32}\text{H}_{26}\text{N}_2\text{O}_2$ : 470.1994. Found: 470.2000.

**Ethyl 3,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (36) and ethyl 4,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (37).** The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 56 mg (84%) of a 1:2.4 inseparable mixture of the indicated compounds as a yellow solid. **Ethyl 3,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-4-carboxylate** (minor isomer):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49 (t,  $J = 7.2$  Hz), 2.78 (s), 3.81 (s), 4.56 (q,  $J = 7.2$  Hz), 8.11 (d); all other peaks overlap with the peaks of the major isomer. **Ethyl 4,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate** (major isomer):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (t,  $J = 7.2$  Hz, 3H), 2.99 (s, 3H), 4.19 (s, 3H), 4.51 (q,  $J = 7.2$  Hz, 2H), 7.37 (m, 1H), 7.46 (d,  $J = 8.4$  Hz, 1H), 7.58 (m, 1H), 9.20 (s, 1H). Additional spectral data from the mixture:  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.3, 14.4, 15.3, 22.8, 30.7, 32.8, 61.8, 61.9, 109.2, 109.3, 111.9, 117.0, 118.7, 120.3, 120.6, 120.8, 121.0, 127.0, 127.4, 140.1, 141.6, 141.9, 142.2, 142.4, 144.2, 145.4, 151.0, 167.9, 168.7. The regiochemistry of carbolines **36** and **37** was determined from the NOESY spectrum of the mixture. IR (neat,  $\text{cm}^{-1}$ ) 2980, 1722; HRMS calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ : 268.1212. Found: 268.1217.

**3,4-Diphenyl-5*H*-pyrido[4,3-*b*]indole (41).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 54 mg (68%) of the indicated compound as a white solid: mp 316-317  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.22 (m, 3H), 7.32-7.50 (m, 10H), 8.19 (d,  $J = 7.6$  Hz, 1H), 8.37 (s, 1H), 9.36 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  111.0, 118.8, 119.1, 120.9, 121.1, 122.0, 126.9, 127.3, 127.7, 127.8, 129.2, 130.1, 130.3, 136.0, 139.8, 140.4, 141.3, 144.0 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3054, 1595; HRMS calcd for  $\text{C}_{23}\text{H}_{16}\text{N}_2$ : 320.1314. Found: 320.1317.

**Diethyl 5-methyl-5*H*-pyrido[4,3-*b*]indole-3,4-dicarboxylate (45).** The reaction was carried out under Conditions C (Table 3, entry 17) and the mixture was chromatographed using 1:1 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a yellow solid: mp 118-119  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (q,  $J = 7.2$  Hz,

6H), 3.90 (s, 3H), 4.53 (q,  $J = 7.2$  Hz, 2H), 4.58 (q,  $J = 7.2$  Hz, 2H), 7.39 (t,  $J = 7.6$  Hz, 1H), 7.49 (d,  $J = 8.4$  Hz, 1H), 7.62 (t,  $J = 7.6$  Hz, 1H), 8.20 (d,  $J = 8.0$  Hz, 1H), 9.38 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.1, 14.4, 30.5, 62.3, 62.5, 109.6, 116.1, 120.0, 121.2, 121.6, 122.4, 128.5, 140.5, 140.7, 142.2, 142.5, 165.7, 167.7; IR (neat,  $\text{cm}^{-1}$ ) 2983, 1725; HRMS calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ : 326.1267. Found: 326.1273.

**4,5-Dimethyl-3-phenyl-5H-pyrido[4,3-b]indole (47).** The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 33.5 mg (49%) of the indicated compound as a white solid: mp 180-182 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.74 (s, 3H), 4.10 (s, 3H), 7.31 (t,  $J = 7.6$  Hz, 1H), 7.35-7.42 (m, 2H), 7.43-7.58 (m, 5H), 8.13 (d,  $J = 7.6$  Hz, 1H), 9.19 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.7, 32.6, 109.1, 113.1, 118.9, 120.3, 120.6, 121.2, 126.6, 127.5, 128.1, 129.9, 140.1, 141.5, 142.1, 145.1, 155.7. The regiochemistry of carboline 47 was determined from its NOESY spectrum. IR (neat,  $\text{cm}^{-1}$ ) 3054, 1582; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2$ : 272.1314. Found: 272.1318.

**3,5-Dimethyl-4-phenyl-5H-pyrido[4,3-b]indole (48).** The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 34.5 mg (51%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.43 (s, 3H), 3.17 (s, 3H), 7.30 (m, 2H), 7.34-7.38 (m, 2H), 7.44-7.53 (m, 4H), 8.14 (m, 1H), 9.20 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.2, 31.5, 109.1, 118.5, 119.4, 120.2, 120.5, 121.1, 126.4, 128.0, 128.6, 130.6, 137.3, 140.9, 141.8, 143.2, 152.3; IR (neat,  $\text{cm}^{-1}$ ) 3054, 2928, 1587; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2$ : 272.1314. Found: 272.1318.

**5-Methyl-3-phenyl-4-trimethylsilyl-5H-pyrido[4,3-b]indole (49) and 5-methyl-3-phenyl-5H-pyrido[4,3-b]indole (50).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 25 mg (38%) of a 1:5 inseparable mixture of the indicated compounds as a yellow oil. **5-Methyl-3-phenyl-4-trimethylsilyl-5H-pyrido[4,3-b]indole** (minor compound):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.12 (s), 3.98 (s), 9.27 (s); all other peaks overlap with the peaks from compound 50. Fifty mg of the above mixture (collected from two runs) was dissolved in 2 mL of methanol and 10 mg of KOH was added. The mixture was stirred at room temperature for 20 h and checked by TLC, which showed only one spot. The

solvent was removed by vacuum and the residue was chromatographed using 3:1 hexanes/EtOAc to afford 36 mg of compound **50** as a yellow solid. **5-Methyl-3-phenyl-5H-pyrido[4,3-*b*]indole**: mp 106-107 °C (lit.<sup>29</sup> mp 106-107 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.89 (s, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.40-7.46 (m, 2H), 7.49-7.56 (m, 3H), 7.69 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 9.36 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 29.1, 100.6, 108.9, 118.7, 120.6, 120.7, 121.3, 126.7, 127.3, 128.5, 128.8, 140.6, 141.5, 142.3, 146.1, 153.6; IR (neat, cm<sup>-1</sup>) 3054, 1594; HRMS calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>: 258.1157. Found: 258.1161.

**Ethyl 5-methyl-5H-pyrido[4,3-*b*]indole-3-carboxylate (59)**. The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 45 mg (71%) of the indicated compound as a yellow solid: mp 150-151 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.04 (s, 3H), 4.43 (q, *J* = 7.2 Hz, 2H), 7.38 (dt, *J* = 0.9, 7.2 Hz, 1H), 7.63 (dt, *J* = 0.9, 7.2 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 8.29 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 9.41 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 13.9, 60.8, 106.4, 109.9, 120.6, 120.9, 121.2, 121.4, 127.8, 142.1, 142.3, 144.1, 144.8, 165.9 (one sp<sup>3</sup> carbon missing due to overlap); IR (neat, cm<sup>-1</sup>) 3059, 2979, 1713; HRMS calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: 254.1055. Found: 254.1058.

**5-Methoxymethyl-3-*n*-octyl-5H-pyrido[4,3-*b*]indole (61)**. The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 75 mg (92%) of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.87 (t, *J* = 8.8 Hz, 3H), 1.20-1.43 (m, 11H), 1.82 (quintet, *J* = 9.2 Hz, 2H), 3.29 (s, 3H), 5.63 (s, 2H), 7.26 (s, 1H), 7.30 (t, *J* = 10.0 Hz, 1H), 7.50 (m, 2H), 8.10 (d, *J* = 10.0 Hz, 1H), 9.21 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.3, 22.9, 29.5, 29.7, 29.8, 30.7, 32.1, 39.3, 56.6, 74.3, 103.1, 109.8, 118.5, 120.7, 121.5, 122.2, 126.8, 140.8, 142.3, 146.3, 159.1; IR (neat, cm<sup>-1</sup>) 3027, 2986; HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O: 324.2202. Found: 324.2206.

**Ethyl 6-benzyloxy-4-methoxymethyl-9H-pyrido[3,4-*b*]indole-3-carboxylate (62, ZK93423)**. To a 2-dram vial were added β-carboline **66** (50 mg), hydrochloric acid (1 M, 1 mL) and EtOH (2 mL). The mixture was then heated at 70 °C for 24 h, cooled, neutralized with satd. aq. Na<sub>2</sub>CO<sub>3</sub> and extracted with EtOAc.

The organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was removed in vacuum and the residue was purified by chromatography on a silica gel column using 10:1  $\text{CHCl}_3/\text{MeOH}$  to afford 36 mg (80%) of ZK93423 (**62**) as a white solid: mp 167-168 (lit.<sup>18b</sup> 187 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.41 (t,  $J$  = 7.2 Hz, 3H), 3.48 (s, 3H), 4.48 (q,  $J$  = 7.2 Hz, 2H), 5.20 (s, 2H), 5.34 (s, 2H), 7.28-7.45 (m, 5H), 7.50 (d,  $J$  = 7.2 Hz, 2H), 7.87 (d,  $J$  = 2.4 Hz, 1H), 8.79 (s, 1H), 9.55 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 58.2, 61.8, 67.8, 71.0, 108.7, 112.6, 119.5, 121.8, 127.7, 128.0, 128.7, 128.9, 129.2, 133.0, 136.2, 137.2, 137.5, 137.7, 153.8, 167.2; IR (neat,  $\text{cm}^{-1}$ ) 3234, 2981, 1712; HRMS calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$ : 390.1580. Found: 390.1585.

**Isopropyl 6-benzyloxy-4-methoxymethyl-9H-pyrido[3,4-b]indole-3-carboxylate (63, abecarnil).** *i*-PrOH (2 mL) instead of EtOH was used as the solvent to deprotect the *N*-methoxymethyl group of  $\beta$ -carboline **68** (60 mg). Everything else is the same as in the case of  $\beta$ -carboline **66**. The mixture was chromatographed using 10:1  $\text{CHCl}_3/\text{MeOH}$  to afford 51 mg (94%) of abecarnil (**63**) as a white solid: mp 148-149 °C (lit.<sup>30</sup> 150-151 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.40 (d,  $J$  = 6.3 Hz, 6H), 3.47 (s, 3H), 5.20 (s, 2H), 5.30 (s, 2H), 5.37 (m, 1H), 7.28-7.52 (m, 7H), 7.86 (d,  $J$  = 2.4 Hz, 1H), 8.76 (s, 1H), 9.72 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.1, 58.3, 68.1, 69.6, 71.2, 108.8, 112.8, 119.6, 122.0, 127.9, 128.2, 128.7, 128.8 (2), 129.0, 133.3, 136.4, 137.4, 137.6, 153.9, 167.2; IR (neat,  $\text{cm}^{-1}$ ) 3290, 2981, 1706; HRMS calcd for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4$ : 404.1736. Found: 404.1742.

**Ethyl 6-benzyloxy-4,9-bis(methoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (66).** The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 67 mg (62%) of the indicated compound as a pale yellow solid: mp 105-107 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49 (t,  $J$  = 7.2 Hz, 3H), 3.27 (s, 3H), 3.47 (s, 3H), 4.53 (q,  $J$  = 7.2 Hz, 2H), 5.22 (s, 2H), 5.32 (s, 2H), 5.74 (s, 2H), 7.30-7.45 (m, 4H), 7.51 (d,  $J$  = 6.9 Hz, 2H), 7.56 (d,  $J$  = 9.0 Hz, 1H), 7.90 (d,  $J$  = 2.4 Hz, 1H), 8.99 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.7, 56.6, 58.4, 62.0, 67.8, 71.2, 74.7, 109.3, 111.1, 119.6, 122.3, 127.8, 128.3, 128.9, 129.0, 129.3, 131.9, 137.0, 137.3, 138.2,

139.2, 154.5, 167.2. The regiochemistry of carboline **66** was determined from its NOESY spectrum in which the correlation signal between the 4-methoxymethyl group and 5-H was observed. IR (neat,  $\text{cm}^{-1}$ ) 3032, 2928, 1724; HRMS calcd for  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ : 434.1842. Found: 434.1850.

**Ethyl 6-benzyloxy-3,9-bis(methoxymethyl)-9H-pyrido[3,4-*b*]indole-4-carboxylate (67).** The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 26 mg (24%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.46 (t,  $J = 7.2$  Hz, 3H), 3.26 (s, 3H), 3.40 (s, 3H), 4.53 (q,  $J = 7.2$  Hz, 2H), 4.88 (s, 2H), 5.16 (s, 2H), 5.70 (s, 2H), 7.30-7.53 (m, 7H), 7.68 (d,  $J = 2.4$  Hz, 1H), 8.95 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 56.5, 58.6, 62.1, 71.1, 74.6, 75.0, 107.5, 111.1, 120.3, 120.7, 121.4, 126.8, 127.8, 128.2, 128.8, 132.6, 136.8, 137.3, 137.4, 145.6, 154.0, 168.4; IR (neat,  $\text{cm}^{-1}$ ) 3032, 2980, 1728; HRMS calcd for  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ : 434.1842. Found: 434.1850.

**Isopropyl 6-benzyloxy-4,9-bis(methoxymethyl)-9H-pyrido[3,4-*b*]indole-3-carboxylate (68).** The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 64 mg (57%) of the indicated compound as a pale yellow solid: mp 90-92  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (d,  $J = 6.4$  Hz, 6H), 3.26 (s, 3H), 3.45 (s, 3H), 5.22 (s, 2H), 5.26 (s, 2H), 5.40 (m, 1H), 5.73 (s, 2H), 7.31-7.43 (m, 4H), 7.51 (d,  $J = 7.2$  Hz, 2H), 7.55 (d,  $J = 9.2$  Hz, 1H), 7.90 (d,  $J = 2.4$  Hz, 1H), 8.99 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.0, 56.4, 58.1, 67.8, 69.4, 71.0, 74.5, 109.1, 110.9, 119.4, 122.1, 127.7, 128.0, 128.1, 128.7, 129.0, 131.9, 136.8, 137.1, 137.9, 140.0, 154.2, 166.9. The regiochemistry of carboline **68** was determined from its NOESY spectrum in which the correlation signal between the 4-methoxymethyl group and 5-H was observed. IR (neat,  $\text{cm}^{-1}$ ) 2925, 1717; HRMS calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_5$ : 448.1998. Found: 448.2003.

**Isopropyl 6-benzyloxy-3,9-bis(methoxymethyl)-9H-pyrido[3,4-*b*]indole-4-carboxylate (69).** The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 41 mg (37%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (d,  $J = 6.0$  Hz, 6H), 3.25 (s, 3H), 3.39 (s, 3H), 4.87 (s, 2H), 5.15

(s, 2H), 5.47 (m, 1H), 5.70 (s, 2H), 7.31-7.36 (m, 2H), 7.40 (t,  $J = 7.2$  Hz, 2H), 7.50 (m, 3H), 7.74 (d,  $J = 2.4$  Hz, 1H), 8.94 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.0, 56.5, 58.4, 69.9, 71.1, 74.6, 74.9, 107.5, 111.1, 120.1, 120.8, 121.9, 126.6, 127.8, 128.2, 128.8, 132.6, 136.8, 137.2, 145.3, 154.0, 168.0; IR (neat,  $\text{cm}^{-1}$ ) 2980, 1717; HRMS calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_5$ : 448.1998. Found: 448.2003.

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**Supporting Information Available.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds 7-10, 12-15, 17-22, 26-31, 36-38, 40-42, 45, 47, 48, 59, 61-63 and 66-69; and NOESY spectra for compounds 12 and 13, 21, 22, 36, 37, 47, 66 and 68. This material is included in Appendix A and is also available free of charge via the Internet at <http://pubs.acs.org>.

## References

1. (a) Hino, T.; Nakagawa, M. *J. Heterocycl. Chem.* **1994**, *31*, 625. (b) Baker, B. J. *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 357. (c) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1. (d) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *43*, 6201. (e) Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567. (f) Ohmoto, T.; Koike, K. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1989; Vol. 36, pp. 135-170.
2. (a) Matsuura, N.; Kawachi, T.; Morino, K.; Ohgaki, H.; Sugimura, T.; Takayama, S. *Science*, **1981**, *213*, 346. (b) Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles* **1990**, *30*, 271.
3. For reviews, see: (a) Gribble, G. W.; In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1990; Vol. 39, Chapter 7. (b) Tan, G. T.; Pezzuto, J. M.; In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: 1996; pp. 1-119. For a recent report, see: (c) Nguyen, C. H.; Lavelle, F.; Riou, J. -F.; Bissery, M. -C.; Huel, C.; Bisagni, E. *Anti-Cancer Drug Design* **1992**, *7*, 235.
4. For recent examples, see: (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans I* **1999**, 1505. (b) Suzuki, H.; Unemoto, M.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717. (c) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (d) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (e) Engler, T.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (f) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S. *Heterocycles* **2000**, *53*, 1877. (g) Choshi, T.; Kumada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108. (h) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793. (i) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477. (j) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (k) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.



5. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49.
6. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; Adams, L.; Alo, B. *Synth. Commun.* **1995**, *25*, 3373.
7. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.
8. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Ed. J. Tsuji, Elsevier Press, Lausanne, Switzerland, 1999, pp. 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.
9. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
10. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.
11. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
12. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
13. Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.
14. Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.
15. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.
16. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
17. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.
18. (a) Huang, Q.; He, X.; Ma, C.; Liu, R.; Yu, S.; Dayer, C. A.; Wenger, G. R.; McKernan, R.; Cook, J. M. *J. Med. Chem.* **2000**, *43*, 71. (b) Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B.; McKernan, R.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1998**, *41*, 2537. (c) Huang, Q.; Zhang, W.; Liu, R.; McKernan, R. M.; Cook, J. M. *Med. Chem. Res.* **1996**, *6*,

384. (d) Fryer, R. I.; Wang, C.-G.; Chia, N.-C.; Basile, A. S.; Gu, Z.-Q.; Skolnick, P. *Med. Chem. Res.* **1995**, *5*, 296. (e) Liu, R.; Zhang, P.; McKernan, R. M.; Wafford, K.; Cook, J. M. *Med. Chem. Res.* **1995**, *5*, 700. (f) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 1062.
19. (a) Koek, W.; Patoiseau, J.-F.; Assie, M.-B.; Cosi, C.; Kleven, M. S. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 266. (b) Thompson, S.-A.; Bonnert, T. P.; Whiting, P. J.; Wafford, K. A. *Toxico. Lett.* **1998**, *100*, 233. (c) Haffer, G.; Nickisch, K.; Tilstam, U. *Heterocycles* **1998**, *48*, 993. (d) Scholze, P.; Ebert, V.; Sieghart, W. *Eur. J. Pharmacol.* **1996**, *304*, 155. (e) Witkin, J. M.; Acri, J. B.; Wong, G.; Gleeson, S.; Barrett, J. E. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 87. (f) Wafford, K. A.; Thompson, S. A.; Sikela, J.; Wilcox, A. S.; Whiting, P. *J. Mol. Pharmacol.* **1996**, *50*, 670. (g) Mehta, A. K.; Shank, R. P. *Life Sci.* **1995**, *57*, 2215. (h) Mumford, G. K.; Rush, C. R.; Griffiths, R. R. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 570. (i) Dazzi, L.; Motzo, C.; Imperatoi, A.; Serra, M.; Gessa, G. L.; Biggio, G. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 241. (j) Stephens, D. N.; Schneider, H.; Kehr, W.; Andrews, J. S.; Rettig, K. J.; Truski, L.; Schmiechen, R.; Turner, J. D.; Jensen, L. H.; Petersen, E. N.; Honore, T.; Hansen, J. B. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 334. (k) Truski, L.; Stephens, D. N.; Jensen, L. H.; Petersen, E. N.; Meldrum, S. B.; Patel, S.; Hansen, J. B.; Losher, W.; Schneider, H.; Schmiechen, R. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 344. (l) Krause, W.; Mengel, H.; Nordholm, L. *J. Pharm. Sci.* **1989**, *78*, 622.
20. (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (c) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.
21. Zhang, Y.; Gong, X.; Zhang, H.; Larock, R. C.; Yeung, E. S. *J. Comb. Chem.* **2000**, *2*, 450.

22. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.
23. (a) Kundo, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561. (b) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. (c) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.
24. (a) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969. (b) Lücking, U.; Pfaltz, A. *Synlett.* **2000**, 1261. (c) Trost, B. M.; Chan, C.; Rühler, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.
25. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C. Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.
26. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447.  
We used ethyl acetate, instead of diethyl ether, as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in 55% yield.
27. Ash, W. *J. Chem. Soc.* **1958**, 3887.
28. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495.
29. Prikhod'ko, T.A.; Vasilevskii, S.F.; Shvartsberg, M.S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 2383.
30. Weber, A.; Kennecke, M.; Hilscher, J. C.; Nickisch, K. *Ger. Offen.* **1992**, DE4029389; *Chem. Abstr.* **1991**, *117*, 7912.

## CHAPTER 2. SYNTHESIS OF $\beta$ - AND $\gamma$ -CARBOLINES BY THE PALLADIUM/COPPER-CATALYZED COUPLING AND CYCLIZATION OF TERMINAL ACETYLENES

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### Abstract

A variety of 3-substituted  $\beta$ - and  $\gamma$ -carbolines have been synthesized from *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-bromoindole-3-carboxaldehydes respectively. The coupling of these aldehydes with various terminal acetylenes using cat.  $\text{PdCl}_2(\text{PPh}_3)_2/\text{CuI}$  readily affords the corresponding alkynylindole carboxaldehydes, which have subsequently been converted to the corresponding *tert*-butylimines and cyclized to  $\beta$ - and  $\gamma$ -carbolines by either copper-catalyzed or thermal processes.

### Introduction

Palladium-catalyzed annulation processes have recently proven to be a powerful method for the construction of a wide variety of hetero- and carbocycles in our own laboratories.<sup>1</sup> In addition, the transition metal-mediated,<sup>2</sup> base-promoted,<sup>3</sup> electrophile-induced<sup>4</sup> and thermal<sup>5</sup> cyclization of alkynes, which possess a nucleophile in close proximity to the carbon-carbon triple bond, have also been shown to be very effective for the synthesis of a wide variety of hetero- and carbocycles. In our own laboratories, a variety of isoquinolines, pyridines and naphthyridines have been successfully synthesized by the copper-catalyzed,<sup>6</sup> the palladium-catalyzed<sup>7</sup> and the electrophile-induced<sup>8</sup> cyclization of alkynes having a *tert*-butylimino group in close proximity to the carbon-carbon triple bond.

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as  $\beta$ - and  $\gamma$ -carbolines, respectively, are the key structural units for a variety of biologically important alkaloids.<sup>9</sup> Numerous  $\beta$ - and  $\gamma$ -carbolines have been studied extensively as antitumor agents.<sup>9</sup> The isolation and synthesis of naturally occurring carbolines and the synthesis of  $\beta$ - and  $\gamma$ -carboline derivatives have received considerable attention in the literature<sup>9,10</sup> due to their biological and pharmaceutical importance.

Hibino and Sakamoto have separately reported that substituted  $\beta$ -carbolines and their *N*-oxides can be synthesized readily by heating the corresponding 3-(1-alkynyl)indole-2-carboxaldehydes with  $\text{NH}_3$ <sup>5a</sup> or  $\text{NH}_2\text{OH}$ .<sup>5b,c</sup> The  $\beta$ -carboline *N*-oxides obtained by this method have been further elaborated by Hibino in the total synthesis of naturally occurring  $\beta$ -carboline alkaloids pyridindolols.<sup>5b,c</sup> Recently, Rossi has improved Sakamoto's carboline synthesis to the synthesis of 1,3-disubstituted  $\beta$ -carbolines by employing 2-acyl-3-(1-alkynyl)indoles and  $\text{NH}_3$ .<sup>5d</sup> Similarly,  $\gamma$ -carbolines and their *N*-oxides have also been synthesized by heating the corresponding 2-(1-alkynyl)indole-3-carboxaldehydes with  $\text{NH}_3$  or  $\text{NH}_2\text{OH}$ .<sup>5a,g</sup> The reduction of  $\gamma$ -carbolines *N*-oxides by  $\text{PCl}_3$  readily affords the corresponding  $\gamma$ -carbolines in satisfactory yields.<sup>5g</sup>

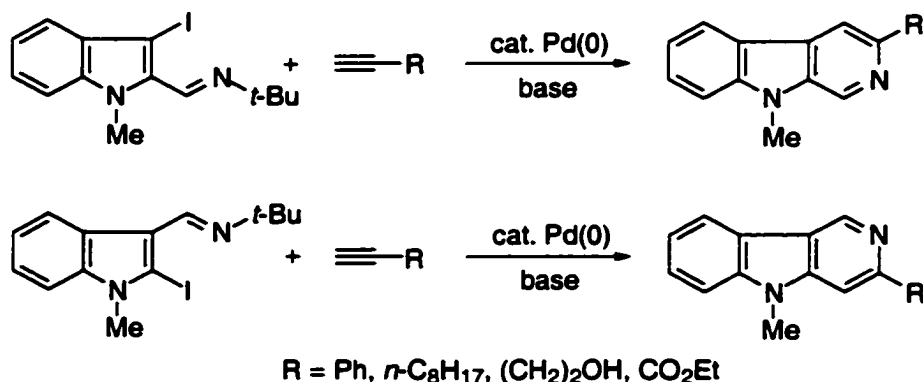
Recently, we have developed a general synthesis of 3,4-disubstituted  $\beta$ - and  $\gamma$ -carbolines by the palladium-catalyzed iminoannulation of *internal* acetylenes.<sup>11</sup> We have also developed a general synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of *terminal* acetylenes.<sup>6</sup> Our interest in the synthesis of carbolines prompted us to examine the synthesis of a variety of 3-substituted  $\beta$ - and  $\gamma$ -carboline derivatives. Our goal during this work was to provide a clean, high yielding and general synthesis of functionalized  $\beta$ - and  $\gamma$ -carbolines, which would provide a useful alternative to Sakamoto's carboline synthesis.<sup>5a</sup> Preliminary studies on this project have previously been communicated.<sup>12</sup> Herein, we wish to report the full details of this successful

synthesis of various  $\beta$ - and  $\gamma$ -carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of *terminal* acetylenes.

## Results and Discussion

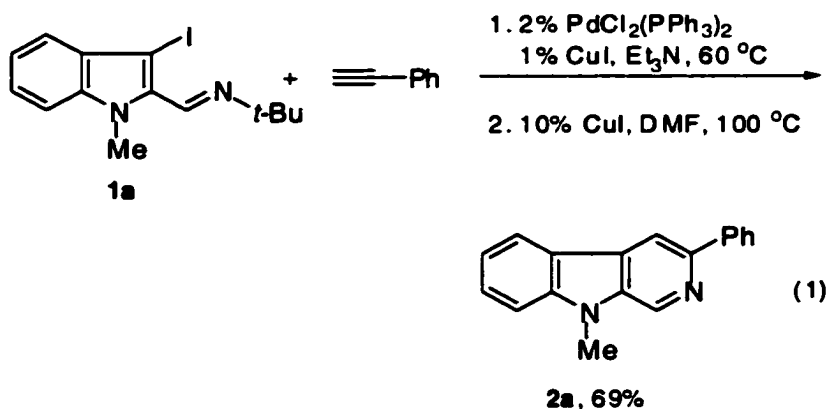
During the course of our investigation of the palladium-catalyzed iminoannulation of *internal* alkynes, we also examined the palladium-catalyzed iminoannulation of *terminal* alkynes. Unfortunately, the annulation of terminal alkynes, such as phenylacetylene, 1-decyne, 3-butyne-1-ol and ethyl propiolate by the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde and 2-iodo-1-methylindole-3-carboxaldehyde (**1a** and **1b**) under our standard conditions<sup>11</sup> for  $\beta$ - and  $\gamma$ -carboline synthesis gave the desired  $\beta$ - and  $\gamma$ -carbolines in relatively low yields in most cases (Scheme 1). Our several attempts to increase the yields of this annulation chemistry failed to give any improved results.

Scheme 1



The reaction sequence for the synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of terminal acetylenes<sup>6</sup> was then examined for the synthesis of  $\beta$ -carbolines by employing the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde (**1a**) and examining its coupling with several terminal alkynes. In short, the palladium/copper-catalyzed coupling of imine **1a** with a terminal acetylene was complete in a few hours as monitored by TLC analysis. The precipitate and the solvent were subsequently removed by filtration and evaporation. DMF and 10 mol % of CuI were then added to the residue. The

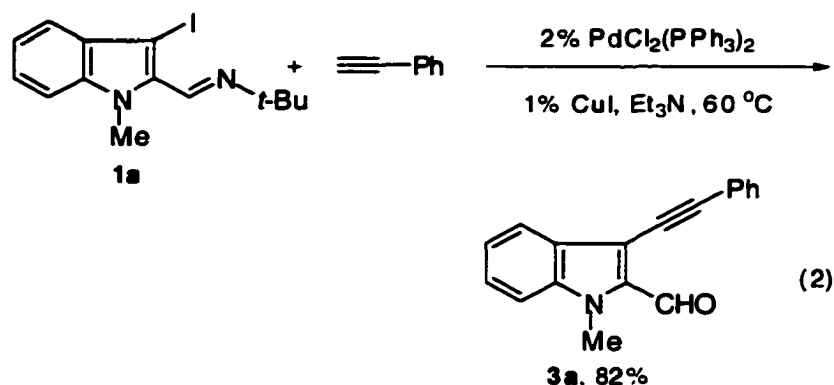
resulting mixture was then heated at 100 °C until the cyclization was complete. Unfortunately, only phenylacetylene gave an acceptable yield (69%) of the desired  $\beta$ -carboline **2a** (eq 1). When other acetylenes, such as 1-decyne, 3-butyne-1-ol and ethyl propiolate were employed, the reactions afforded low yields of the corresponding  $\beta$ -carboline in all cases.



Since the same reaction procedure has proven successful for the synthesis of isoquinolines, one wonders why this reaction procedure does not work well in the  $\beta$ -carboline synthesis. The reasons appear complicated. The palladium/copper-catalyzed Sonogashira coupling<sup>13</sup> of ethyl 3-iodo-1*H*-indole-2-carboxylate and ethyl 3-iodo-1-(methanesulfonyl)indole-2-carboxylate with terminal acetylenes has been reported previously to proceed in relatively low yields.<sup>14</sup> As an analogue to the above carboxylates, imine **1a** might also suffer the problem of low yields when it undergoes the coupling reaction with terminal acetylenes. Moreover, the bulky *tert*-butylimine moiety in imine **1a** might also affect the Sonogashira reaction. Furthermore, the Sonogashira coupling might produce by-products, which cannot be removed in the one-pot process and might interfere with the subsequent copper-catalyzed cyclization.

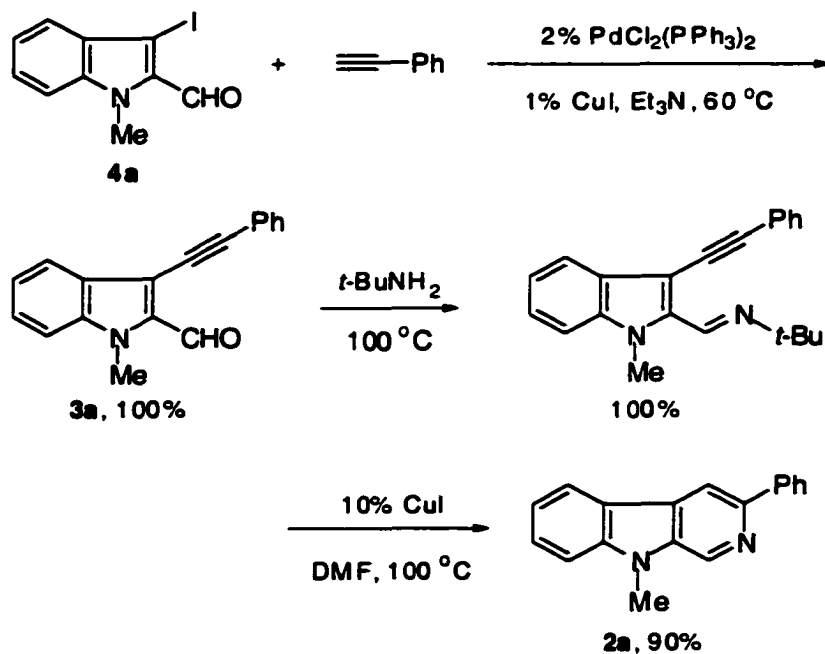
In order to investigate the major factors that cause the low yields of  $\beta$ -carboline products, the coupling product of imine **1a** with phenylacetylene was therefore isolated before it was employed in the subsequent copper-catalyzed cyclization. Instead of the *tert*-butylimine, the alkynylindole aldehyde **3a**, which is

apparently arising from hydrolysis of the corresponding *tert*-butylimine during column chromatography, was isolated in an 82% yield (eq 2). As a control experiment,



the coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with phenylacetylene was performed, affording the same alkynylindole aldehyde **3a** in a 100% yield. The aldehyde **3a** was then quantitatively converted to the corresponding *tert*-butylimine, which was subsequently employed in the copper-catalyzed cyclization, which smoothly afforded the desired  $\beta$ -carboline **2a** in a 90% yield (Scheme 2).

#### Scheme 2



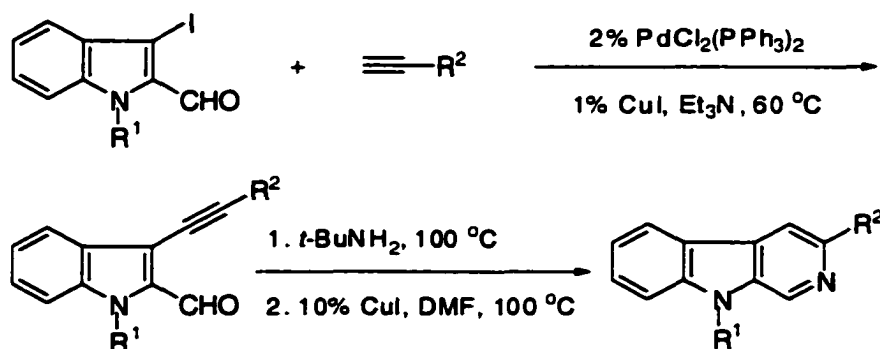
By comparing the results of eq 1 and eq 2 with those of Scheme 2, we conclude that the bulky *tert*-butylimine moiety does affect the Sonogashira coupling



of imine **1a** with phenylacetylene, and the by-products generated by the Sonogashira coupling of imine **1a** with phenylacetylene also interfere with the subsequent copper-catalyzed cyclization. These problems might also happen in the  $\beta$ -carboline synthesis employing other acetylenes under the standard reaction sequence of our isoquinoline synthesis, which afforded low yields of  $\beta$ -carbolines in all cases, as mentioned previously.

As we have seen, the control experiment employing aldehyde **4a** and phenylacetylene gave a higher total yield (90%) of the desired  $\beta$ -carboline **2a** (Table 1, entry 1) than the reaction employing the sequence of our earlier isoquinoline synthesis (69%). The transformation of aldehyde to the corresponding *tert*-butylimine is essentially quantitative, as observed in our previous work.<sup>1m,1n,6,11</sup> We have thus simply changed the reaction sequence to that of the control experiment, which requires no further purification and characterization of the *tert*-butylimines. This ensures essentially pure starting materials for each step (Scheme 3). The results of this study are summarized in Table 1.

**Scheme 3**



As shown in Table 1, the palladium/copper-catalyzed Sonogashira coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with a variety of terminal acetylenes afforded excellent yields of the corresponding 3-alkynyl-1-methylindole-2-carboxaldehydes **3a-g**, which were then converted into the corresponding *tert*-butylimines, which were subsequently subjected to copper-catalyzed cyclization to generate the desired 3-substituted  $\beta$ -carbolines **2a-g** in excellent yields (entries 1-7).

Aryl-, alkenyl-, and alkyl-substituted terminal acetylenes have proven successful in this  $\beta$ -carboline synthesis (entries 1-4). Moreover, hydroxy-, ester-, and cyano-substituted terminal alkynes also afforded the coupling products and the corresponding  $\beta$ -carbolines in excellent yields (entries 5-7).

When a silyl-substituted terminal alkyne, triethylsilylacetylene, was employed, the coupling successfully afforded a 100% yield of the desired alkynylindole **3h** (entry 8). However, the copper-catalyzed cyclization didn't afford any of the desired triethylsilyl-substituted  $\beta$ -carboline. Instead, a 28% yield of the desilylated  $\beta$ -carboline **2h** was isolated by column chromatography, along with a 70% yield of the desilylated intermediate 2-*tert*-butyl-9-methyl-9*H*-pyrido[3,4-*b*]indolium hydroxide, which was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and mass spectrometry. The  $\beta$ -carbolinium salt thermally eliminates the *tert*-butyl group to form the  $\beta$ -carboline **2h** in a 58% yield at 130 °C after 72 h. To avoid the difficulty in isolating the highly polar  $\beta$ -carbolinium salt, after the copper-catalyzed cyclization reaction was complete as judged by TLC analysis, the reaction mixture was continuously heated at 130 °C for 72 h. Unfortunately, the  $\beta$ -carboline **2h** was isolated in only a 41% yield by this process (entry 8).

When an acetylene containing a bulky group, namely 1-ethynylcyclohexanol was employed, the coupling successfully gave the alkynylindole **3i** in a 100% yield (entry 9). Surprisingly, the cyclization didn't afford any of the desired product. Instead, the  $\beta$ -carboline **2h**, which had lost the cyclohexane ring, and the same  $\beta$ -carbolinium salt that was formed in the silyl case were detected by TLC analysis and  $^1\text{H}$  NMR spectroscopy. To avoid isolation of the extremely polar  $\beta$ -carbolinium salt, the reaction mixture was heated at 130 °C for 72 h to eliminate the *tert*-butyl group present in the salt. Unfortunately, only a 35% yield of the  $\beta$ -carboline **2h** was isolated (entry 9). Again, loss of the hydroxycyclohexyl group is the predominant reaction.

**Table 1. Synthesis of  $\beta$ -Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes**

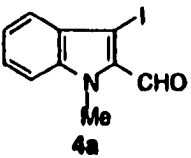

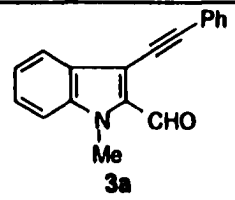
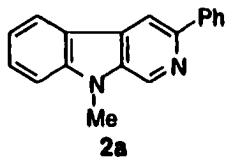
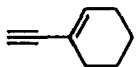
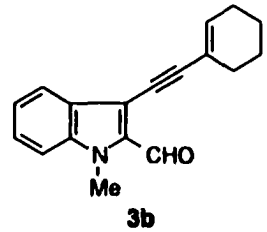
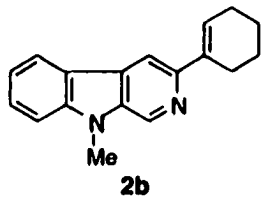

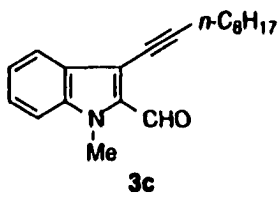
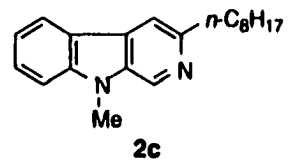
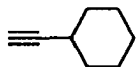
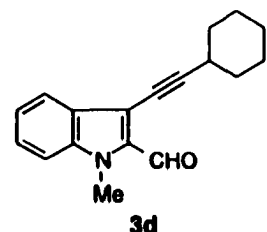
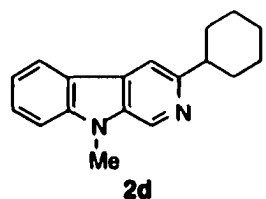
entry	aldehyde	alkyne	alkynyldole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
1				3	100		20	90
2				18	98		24	93
3				16	88		24	93
4				16	96		40	93

Table 1. Continued

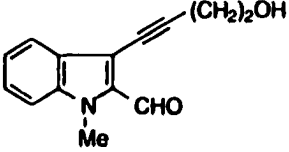
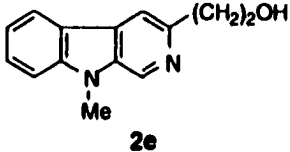
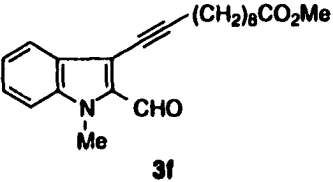
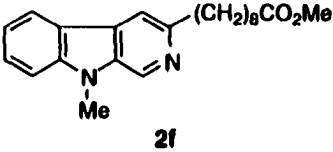
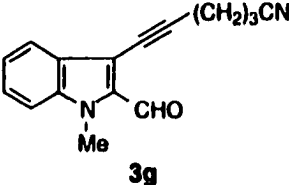
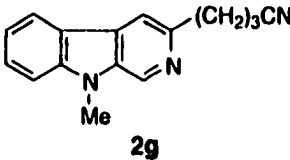
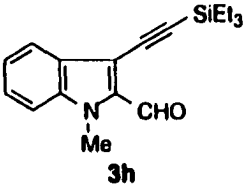
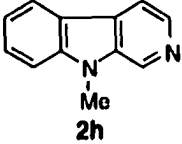
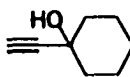
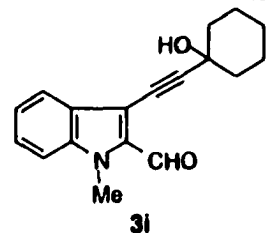
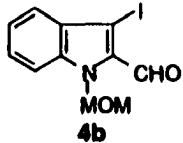
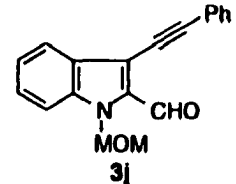
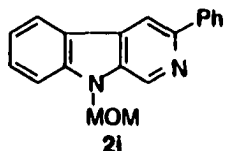
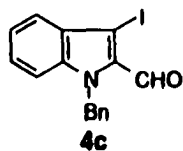
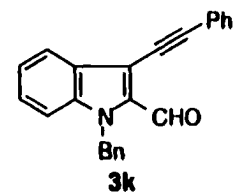
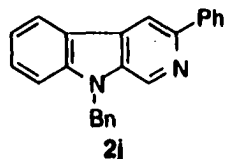
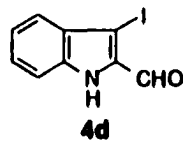
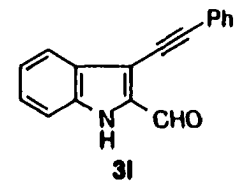
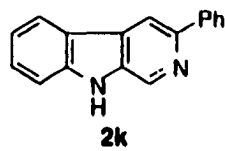
entry	aldehyde	alkyne	alkynylindole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
5		$\equiv-(\text{CH}_2)_2\text{OH}$	 3e	16	87	 2e	15	95
6		$\equiv-(\text{CH}_2)_8\text{CO}_2\text{Me}$	 3f	16	98	 2f	18	95
7		$\equiv-(\text{CH}_2)_3\text{CN}$	 3g	16	82	 2g	20	88
8		$\equiv-\text{SiEt}_3$	 3h	16	100	 2h	92 <sup>c</sup>	41

Table 1. Continued

entry	imine	alkyne	alkynylindole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
9			 <b>3i</b>	18	100	<b>2h</b>	92 <sup>c</sup>	35
10	 <b>4b</b>	$\equiv$ -Ph	 <b>3j</b>	16	95	 <b>2i</b>	20	100
11	 <b>4c</b>	$\equiv$ -Ph	 <b>3k</b>	18	89	 <b>2j</b>	18	99
12	 <b>4d</b>	$\equiv$ -Ph	 <b>3l</b>	4	93	 <b>2k</b>	24	trace <sup>d</sup>

<sup>a</sup> The reaction time was not optimized. Some of the coupling reactions in this study might be complete in a much shorter time than listed, as is the case in entries 1 and 12. <sup>b</sup> Isolated yields. <sup>c</sup> The reaction was heated at 100 °C for 20 h and subsequently at 130 °C for 72 h. <sup>d</sup> A 36% yield of **3l** was isolated.

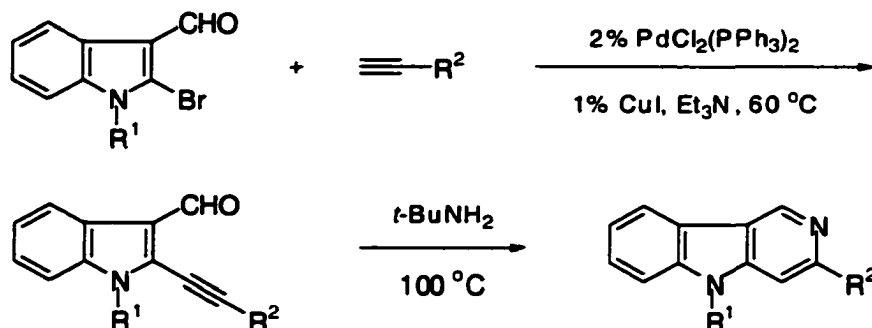
An electron-deficient terminal acetylene, ethyl propiolate, was also employed in the palladium/copper-catalyzed coupling process. Unfortunately, the reaction didn't afford any significant amount of the coupling product. Two electron-rich terminal acetylenes, ethoxyacetylene and 2-ethynylbenzofuran, also failed to produce the coupling products in decent yields. Presumably, these terminal alkynes are too reactive and thus polymerize under the coupling conditions.<sup>15</sup>

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted iodoindoles **4b** and **4c** were employed in the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of phenylacetylene. The coupling process afforded the alkynylindole aldehydes **3j** and **3k** in 95% and 89% yields, and the cyclization generated the desired  $\beta$ -carbolines **2i** and **2j** in 100% and 99% yields, respectively (entries 10 and 11). The unprotected iodoindole, 3-iodo-1*H*-indole-2-carboxaldehyde (**4d**) undergoes palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **3l** in a 92% yield. Unfortunately, the subsequent cyclization only afforded a trace of the desired  $\beta$ -carboline **2k**. A messy reaction was observed and a 36% of the aldehyde **3l** was recovered (entry 12).

Encouraged by our success with the  $\beta$ -carboline synthesis, we have also investigated the palladium/copper-catalyzed coupling of terminal acetylenes using *N*-substituted 2-bromoindole-3-carboxaldehydes in order to synthesize various 3-substituted  $\gamma$ -carbolines. The palladium/copper-catalyzed coupling of phenylacetylene and 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) was first examined. The coupling reaction proceeded smoothly, producing the desired alkynylindole **6a** in a 93% yield. The alkynylindole **6a** was then heated with *tert*-butylamine at 100 °C in a sealed tube. To our pleasant surprise, instead of the corresponding *tert*-butylimine, the  $\gamma$ -carboline product **7a** was detected by TLC analysis after 20 h and subsequently isolated in a 92% yield (Table 2, entry 1). This preliminary result prompted us to investigate the scope of this synthesis of 3-substituted  $\gamma$ -carbolines by the palladium/copper-catalyzed coupling and thermal

cyclization of terminal acetylenes (Scheme 4). The results of this study are summarized in Table 2.

**Scheme 4**



As shown in Table 2, the palladium/copper-catalyzed Sonogashira coupling of 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) with a variety of terminal acetylenes afforded good to excellent yields of the corresponding 2-alkynyl-1-methylindole-3-carboxaldehydes, which were then converted to the *tert*-butylimines, which subsequently underwent thermal cyclization *in situ* to generate the desired 3-substituted  $\gamma$ -carbolines in good to excellent yields (entries 1-6). As we expected, aryl-, alkenyl-, alkyl-substituted terminal acetylenes have again proven successful in this  $\gamma$ -carboline synthesis (entries 1-4). Unfortunately, 3-propyn-1-ol, which was quite successful in the  $\beta$ -carboline synthesis, didn't give any significant yield of the coupling product. However, another hydroxy-containing alkyne, 10-undecyn-1-ol afforded Sonogashira coupling product **6e** and the corresponding  $\gamma$ -carboline **7e** in 61% and 72% yields, respectively (entry 5). Methyl 10-undecynoate also underwent coupling and cyclization successfully, affording an 86% yield of coupling product **6f** and an 88% yield of the  $\gamma$ -carboline product **7f** (entry 6). Surprisingly again, 5-cyano-1-pentyne, which proved successful in our  $\beta$ -carboline synthesis, failed to give any decent yield of the Sonogashira coupling product.

Triethylsilylacetylene undergoes the coupling smoothly, generating a 94% yield of alkynylindole aldehyde **6g**. However, the subsequent thermal cyclization afforded none of the desired  $\gamma$ -carboline. Instead, an 86% yield of the desilylated

**Table 2. Synthesis of  $\gamma$ -Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes**

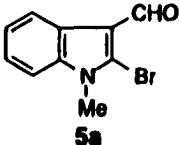

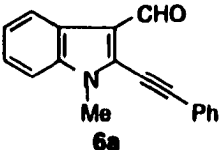
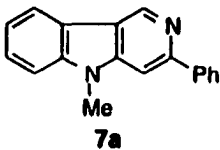
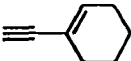
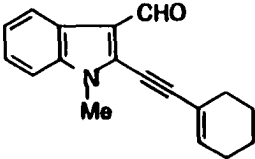
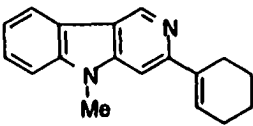
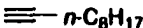
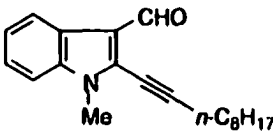
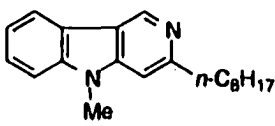
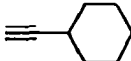
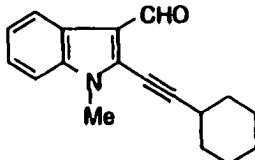
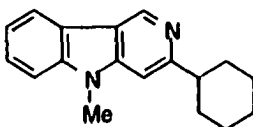
entry	aldehyde	alkyne	alkynylindole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
1	 <b>5a</b>		 <b>6a</b>	24	93	 <b>7a</b>	20	92
2			 <b>6b</b>	20	98	 <b>7b</b>	40	93
3			 <b>6c</b>	20	82	 <b>7c</b>	24	87
4			 <b>6d</b>	4	89	 <b>7d</b>	40	83



Table 2. Continued

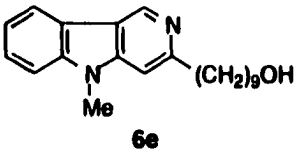
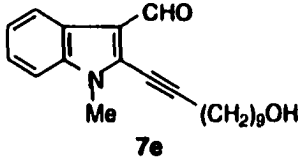
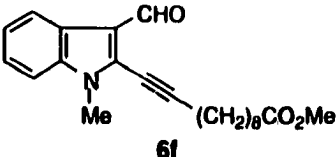
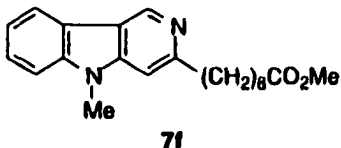
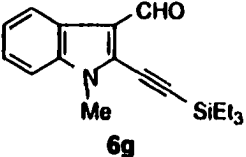
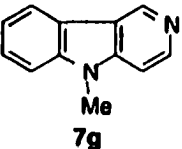
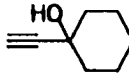
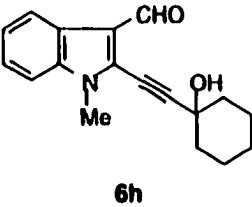
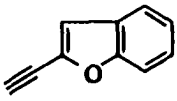
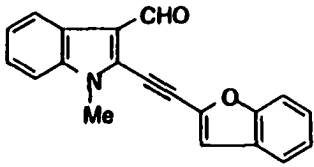
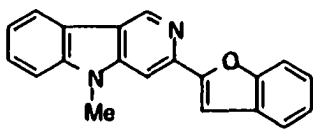
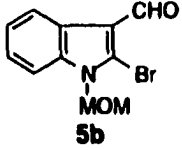

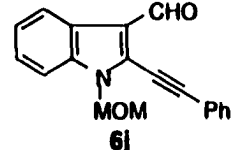
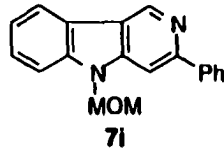
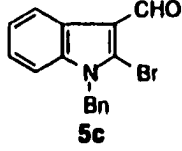

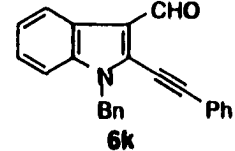
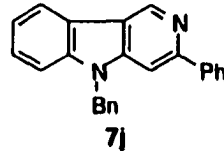
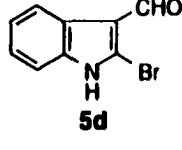

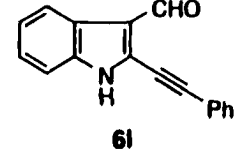
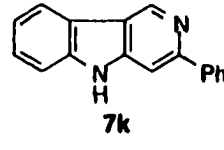
entry	aldehyde	alkyne	alkynylindole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
5		$\equiv-(\text{CH}_2)_9\text{OH}$	 6e	16	61	 7e	20	72
6		$\equiv-(\text{CH}_2)_8\text{CO}_2\text{Me}$	 6f	16	86	 7f	20	88
7		$\equiv-\text{SiEt}_3$	 6g	16	94	 7g	92 <sup>c</sup>	41
8			 6h	18	87	7g	92 <sup>c</sup>	40

Table 2. Continued

entry	imine	alkyne	alkynyldindole	time (h) <sup>a</sup>	% yield <sup>b</sup>	product	time (h) <sup>a</sup>	% yield <sup>b</sup>
9			 6i	6 <sup>d</sup>	78 <sup>d</sup>	 7h	40	95
10	 5b		 6j	20	97	 7i	18	80
11	 5c		 6k	18	73	 7j	22	90
12	 5d		 6l	14	64	 7k	20	49

<sup>a</sup> The reaction time was not optimized. Some of the coupling reactions might be complete in a much shorter time, as is the case in entries 4 and 9. <sup>b</sup> Isolated yields. <sup>c</sup> The reaction was run at 100 °C for 22 h and subsequently at 130 °C for 72 h. <sup>d</sup> An unseparable mixture of 67% of 6i and 33% of 5a was isolated after 3 h, which was subjected to another Sonogashira coupling for 3 h.

salt, 2-*tert*-butyl-5-methyl-5*H*-pyrido[4,3-*b*]indolium hydroxide, was observed and confirmed by  $^1\text{H}$  NMR spectroscopy and mass spectrometry. To avoid isolation of the extremely polar  $\gamma$ -carbolinium salt, a process similar to that of the corresponding  $\beta$ -carboline system was carried out. After the cyclization was complete as judged by TLC analysis, the solvent *tert*-butylamine was removed by vacuum and DMF was added to the residue. The mixture was then heated at 130 °C for 72 h.

Unfortunately, only a 41% yield of the  $\gamma$ -carboline **7g** was isolated (entry 7).

When 1-ethynylcyclohexanol was employed, the coupling was successful, producing an 87% yield of the alkynylindole **6h**, which was then heated with *tert*-butylimine.

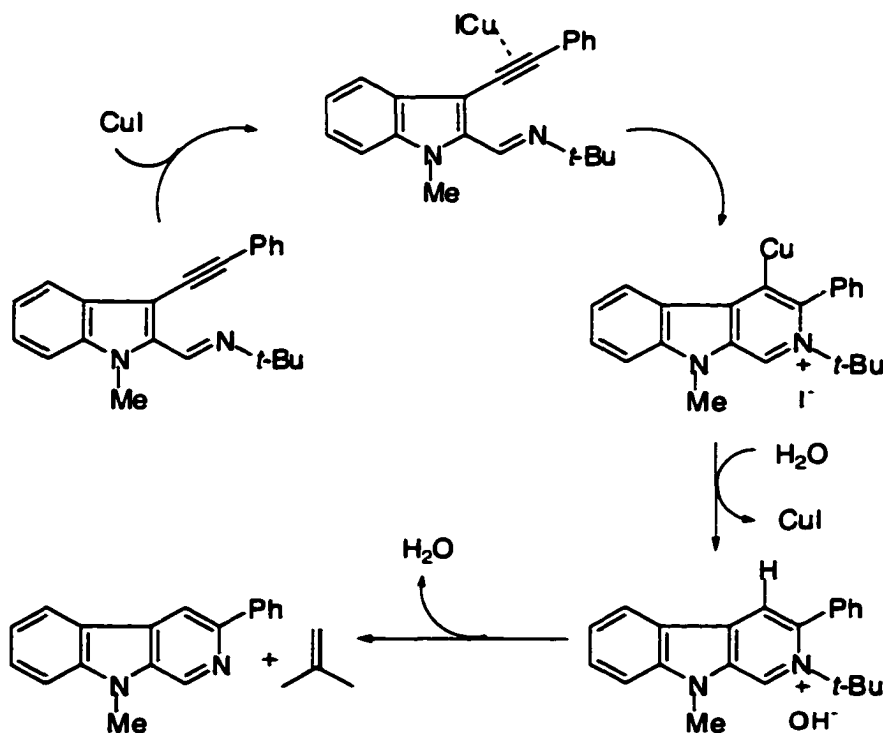
Surprisingly, neither the desired  $\gamma$ -carboline, nor the  $\gamma$ -carboline minus the hydroxycyclohexyl group or the  $\gamma$ -carbolinium salt were observed. Instead, the corresponding *tert*-butylimine was detected after 24 h by TLC analysis, which was further confirmed by  $^1\text{H}$  NMR spectroscopy, and the imine was isolated in a 100% yield after removal of the solvent *tert*-butylamine by vacuum. CuI (10 mol %) and DMF were then added to the *tert*-butylimine in order to facilitate the cyclization, as was done in the  $\beta$ -carboline synthesis. Interestingly, the *tert*-butylimine completely disappeared and the  $\gamma$ -carbolinium salt minus the hydroxycyclohexyl group, the same salt as we obtained earlier in the silyl case, was observed after only 2 h by TLC analysis and  $^1\text{H}$  NMR spectroscopy. Apparently, CuI accelerates the fragmentation process.<sup>16</sup> The reaction mixture was then heated at 130 °C for 72 h, and a 40% yield of the  $\gamma$ -carboline **7g** was isolated (entry 8).

Similar to our observations in the  $\beta$ -carboline synthesis, the electron-deficient alkyne ethyl propiolate and the electron-rich alkyne ethoxyacetylene failed to afford significant amounts of the coupling products. Interestingly, another electron-rich terminal alkyne, 2-ethynylbenzofuran, produced the coupling product in a 67% yield, along with a 33% yield of the starting bromide as an unseparable mixture. This mixture was employed in another Sonogashira coupling under our standard conditions, affording cleanly the alkynylindole **6i** in a 78% total yield. Surprisingly, if the amount of 2-ethynylbenzofuran was increased from 1.2 to 3 equivs, the coupling

gave a messier reaction and a lower yield (56%) of the alkynylindole **6i**. The resulting alkynylindole **6i** was subjected to the subsequent thermal cyclization, which produced a 95% yield of the desired  $\gamma$ -carboline **7h** (entry 9).

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted bromoindoles **5b** and **5c** were employed in the palladium/copper-catalyzed coupling and thermal cyclization of phenylacetylene. The coupling afforded the alkynylindole aldehydes **6j** and **6k** in 97% and 73% yields, and the cyclization generated the desired  $\gamma$ -carbolines **7i** and **7j** in 80% and 90% yields, respectively (entries 10 and 11). The unprotected indolealdehyde, 2-bromo-1*H*-indole-3-carboxaldehyde (**5d**), underwent palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **6l** in a 64% yield. Unfortunately, the subsequent thermal cyclization only afforded a 49% yield of the desired  $\gamma$ -carboline **7k** (entry 12).

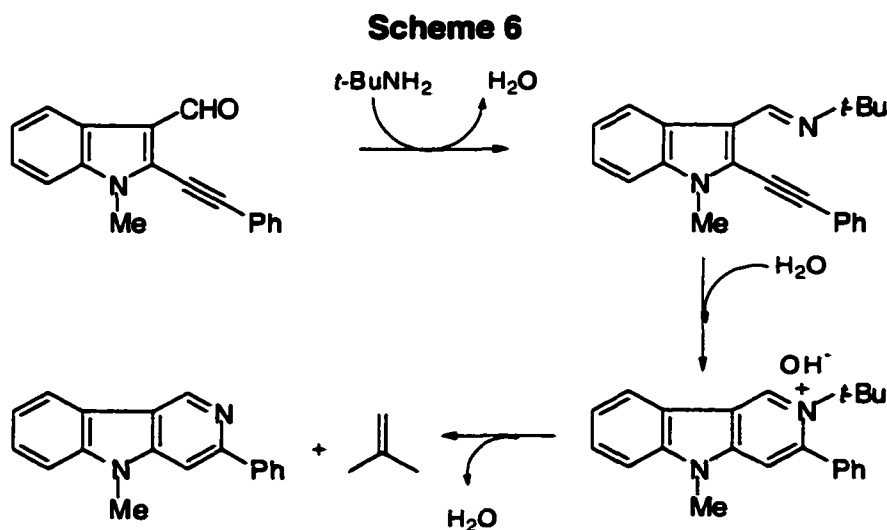
**Scheme 5**



We believe that a reasonable mechanism for the synthesis of  $\beta$ -carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of

terminal acetylenes involves CuI coordinating to the carbon-carbon triple bond of the *tert*-butylimine, followed by intramolecular nucleophilic attack of the nitrogen of the imine moiety on the carbon-carbon triple bond forming a  $\beta$ -carbolinium intermediate. This copper intermediate is presumably protonated by spurious amounts of water present in the system, regenerating CuI and producing a carbolinium salt, which then relieves the strain resulting from the interaction with the substituent present on the neighboring carbon by fragmentation of the *tert*-butyl group,<sup>17</sup> producing the  $\beta$ -carboline (Scheme 5).

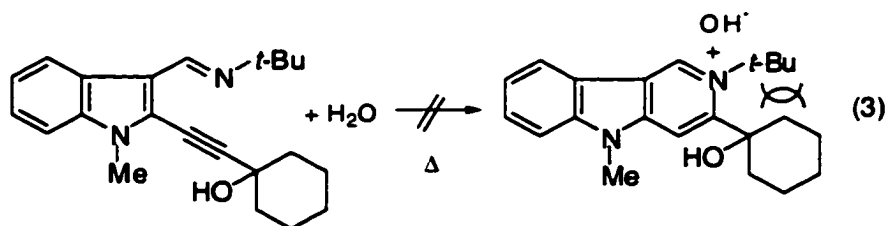
We also propose a mechanism for the synthesis of  $\gamma$ -carbolines by the palladium/copper-catalyzed coupling and thermal cyclization of terminal acetylenes (Scheme 6). Specifically, the nitrogen of the imine moiety nucleophilically attacks the carbon-carbon triple bond of the *tert*-butylimine, capturing a proton from water to form the  $\gamma$ -carbolinium salt. The *tert*-butyl group in the  $\gamma$ -carbolinium salt apparently fragments to relieve the strain resulting from the interaction with the substituent present in the 3-position.



It is now easy to understand why the copper-catalyzed cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **3h** and the thermal cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **6g** both afforded the corresponding desilylated carbolinium salts.<sup>18</sup> In these two cases, the triethylsilyl

group undergoes protodesilylation under the reaction conditions. Due to the lack of strain between the *tert*-butyl group and the hydrogen in the 3-position, the *tert*-butyl group either fragments incompletely ( $\beta$ -carboline synthesis), or survives without fragmentation ( $\gamma$ -carboline synthesis) under the standard reaction conditions. However, a higher temperature (130 °C) promotes thermal fragmentation of the *tert*-butyl group, as discussed previously.

It is also understandable that when the bulky 1-hydroxycyclohexyl substituted alkynylindole **6h** was subjected to thermal cyclization under the standard conditions, which are successful for the less bulky substituted alkynylindoles **6a-f**, the reaction produced none of the desired  $\gamma$ -carboline, but afforded the corresponding *tert*-butylimine instead. Apparently, the steric interaction between two neighboring bulky groups disfavors formation of the  $\gamma$ -carbolinium salt intermediate (eq 3). The presence of a catalytic amount of CuI

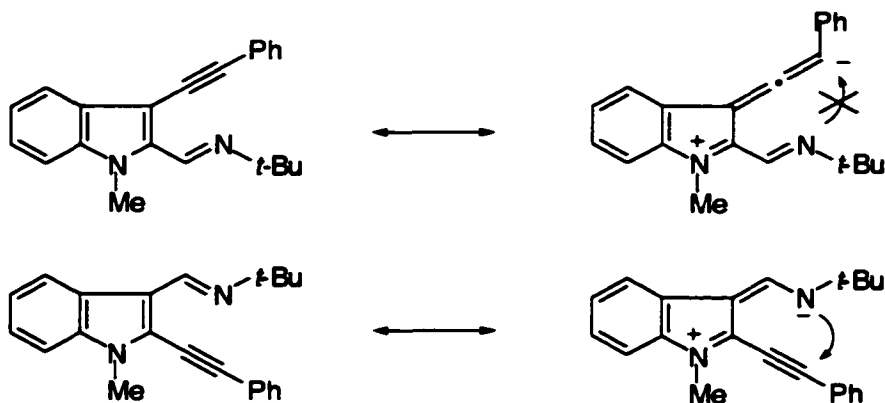


apparently accelerates loss of the hydroxycyclohexyl group,<sup>16</sup> as we observed disappearance of the *tert*-butylimine of alkynylindole **6h** and formation of the fragmented  $\gamma$ -carbolinium salt in only 2 h. As discussed previously, the fragmentation process also occurs during the corresponding  $\beta$ -carboline synthesis, which might also be catalyzed by the presence of CuI.

It is worth noting that the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **3** can donate electrons through resonance to increase the electron density on the carbon-carbon triple bond. Therefore, the carbon-carbon triple bond is less electrophilic, and thus requires CuI coordination to decrease the electron density. On the contrary, the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **5** donates electrons through resonance to the

nitrogen of the imine moiety, which consequently becomes a better nucleophile. As a result, *in situ* nucleophilic attack of the imino-nitrogen on the carbon-carbon triple bond proceeds smoothly under the thermal conditions used to produce the imine (Scheme 7).

Scheme 7



### Conclusions

In conclusion, an efficient palladium/copper-catalyzed coupling and copper-catalyzed or thermal-promoted synthesis of  $\beta$ - and  $\gamma$ -carbolines has been developed. A wide variety of functionalized terminal acetylenes participate in this process to afford the desired nitrogen heterocycles in good to excellent yields. However, triethylsilyl- and 1-hydroxycyclohexyl-substituted acetylenes generate the desilylated and fragmented carbolines in moderate yields at an elevated temperature.

### Experimental Section

**General.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially. 3-Iodo-1-(methoxymethyl)indole-2-carboxaldehyde<sup>19</sup> (**4b**), 3-iodo-1*H*-indole-2-carboxaldehyde<sup>19</sup> (**4d**), 2-bromo-1*H*-indole-3-carboxaldehyde<sup>20</sup> (**5d**) and methyl 1-

undecynoate<sup>21</sup> were prepared according to previous literature procedures. 3-Iodo-1-methylindole-2-carboxaldehyde (**4a**), 2-bromo-1-methylindole-3-carboxaldehyde (**5a**), 2-bromo-1-(methoxymethyl)indole-3-carboxaldehyde (**5b**), 3-iodo-1-methylindole-2-methylene-*tert*-butylamine and 2-iodo-1-methylindole-3-methylene-*tert*-butylamine have been reported previously.<sup>11</sup> Following is the preparation of the starting materials 2-ethynylbenzofuran, 1-benzyl-3-iodoindole-2-carboxaldehyde (**4c**) and 1-benzyl-2-bromoindole-3-carboxaldehyde (**5c**).

**2-Ethynylbenzofuran.** *tert*-Butyl lithium (6.5 mL, 1.7 M in pentane, 11 mmol) was added to a solution of benzofuran (1.18 g, 10 mmol) in dry ether (20 mL) at -78 °C. The mixture was stirred for 30 min and a solution of I<sub>2</sub> (2.85 g, 11 mmol) in dry ether (30 mL) was added. The mixture was stirred for another 30 min, allowed to warm to room temperature, diluted with satd aq NH<sub>4</sub>Cl, and extracted with ether. The organic solution was washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and water, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated under reduced pressure, affording 2.32 g (95%) of crude 2-iodobenzofuran as a yellow oil in > 90% purity, which was confirmed by <sup>1</sup>H NMR spectroscopy.

To 2.32 g of crude 2-iodobenzofuran was added CuI (19 mg, 1 mol %), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (133 mg, 2 mol %), Et<sub>3</sub>N (20 mL) and trimethylsilylacetylene (1.12 g, 11 mmol, 1.2 equiv). The mixture was flushed with Ar and heated at 60 °C for 3 h. The precipitate and solvent were filtered and evaporated, affording 2.24 g (100%) of crude 2-(trimethylsilylethynyl)benzofuran as a yellow oil, which was then dissolved in CH<sub>3</sub>OH (20 mL) containing KOH (0.533 g, 9.5 mmol, 1 equiv). The mixture was stirred at room temperature for 30 min. The solvent was evaporated by vacuum and the residue was purified by column chromatography using hexanes, affording 0.86 g (64% based on benzofuran) of 2-ethynylbenzofuran as a pale yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.49 (s, 1H), 7.00 (d, *J* = 0.4 Hz, 1H), 7.24 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.35 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.46 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.56 (dd, *J* = 8.0, 0.8 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 74.2, 83.5, 111.4, 112.7, 121.4, 123.5, 126.0, 127.2, 137.7, 154.8.



**1-Benzyl-3-iodoindole-2-carboxaldehyde (4c).** This aldehyde was prepared as a white solid in 100% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde<sup>19</sup> only employing 3-iodo-1*H*-indole-2-carboxaldehyde and benzyl iodide: mp 114-115 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.84 (s, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.20-7.27 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.43 (dt, *J* = 8.0, 0.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 10.00 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 48.0, 111.4, 122.1, 123.9, 126.6, 127.6, 128.5, 128.7, 130.0, 131.1, 137.4, 140.4, 184.5.

**1-Benzyl-2-bromoindole-3-carboxaldehyde (5c).** This aldehyde was prepared as a pale yellow solid in 97% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde<sup>19</sup> only employing 2-bromo-1*H*-indole-3-carboxaldehyde and benzyl iodide: mp 124-126 °C (lit.<sup>22</sup> mp 125 °C); the <sup>1</sup>H NMR spectral data are consistent with those previously reported;<sup>22</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 48.9, 110.6, 121.5, 123.7, 124.5, 125.7, 126.3, 126.6, 126.7, 128.3, 129.3, 135.4, 137.3, 185.8.

**General Procedure for the Synthesis of  $\beta$ -Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes.** CuI (1.0 mg, 1 mol %), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 2 mol %), the *N*-substituted 3-iodoindole-2-carboxaldehyde (0.50 mmol), and Et<sub>3</sub>N (4 mL) were placed in a 2-dram vial. The contents were stirred for 1 min and the appropriate acetylene (0.60 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 60 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The precipitate was removed by filtration. The solvent was evaporated under reduced pressure and the coupling product was isolated by chromatography on a silica gel column. A small amount of the coupling product was used for characterization. The remaining material was transferred to another 2-dram vial, and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for 24 h and then cooled, diluted with ether, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The solvent was

evaporated under reduced pressure, giving the corresponding *tert*-butylimine. The *tert*-butylimine was transferred to a 2-dram vial, CuI (10 mol %) and DMF (10 mL/mmol) were added. The mixture was flushed with Ar and heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. DMF was removed under reduced pressure by rotary evaporation and the  $\beta$ -carboline was isolated by column chromatography.

**General Procedure for the Synthesis of  $\gamma$ -Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes.** The *N*-substituted 2-bromoindole-3-carboxaldehyde (0.50 mmol), Et<sub>3</sub>N (4 mL) and DMF (0.4 mL, to increase the solubility of the aldehyde) were used. The rest of the procedure is identical to that used for the coupling reactions in the  $\beta$ -carboline synthesis. A small amount of the coupling product was used for characterization. The remaining material was transferred to a 2-dram vial and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The solvent was evaporated under reduced pressure and the  $\gamma$ -carboline was isolated by column chromatography.

### Alkynylindoles Prepared

**1-Methyl-3-(phenylethynyl)indole-2-carboxaldehyde (3a).** The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 130 mg (100%) of the indicated compound as a yellow solid: mp 87-89 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.07 (s, 3H), 7.25 (m, 1H), 7.37 (m, 4H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.59 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 10.26 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  31.9, 80.4, 97.0, 110.6, 111.9, 121.7, 122.3, 123.1, 127.7, 127.8, 128.5, 128.6, 131.6, 135.5, 139.6, 182.3; IR (neat, cm<sup>-1</sup>) 2207, 1669; HRMS calcd for C<sub>18</sub>H<sub>13</sub>NO: 259.0997. Found: 259.1001.

**3-(1-Cyclohexenylethynyl)-1-methylindole-2-carboxaldehyde (3b).** The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 129 mg

(98%) of the indicated compound as a yellow solid: mp 71-73 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.61-1.69 (m, 2H), 1.69-1.97 (m, 2H), 2.18-2.21 (m, 2H), 2.29-2.32 (m, 2H), 4.08 (s, 1H), 6.31 (m, 1H), 7.22 (m, 1H), 7.37 (d,  $J$  = 8.4 Hz, 1H), 7.45 (m, 1H), 7.82 (d,  $J$  = 8.4 Hz, 1H), 10.19 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.5, 21.3, 24.8, 28.3, 30.7, 76.5, 98.0, 109.4, 111.7, 119.7, 120.4, 121.2, 126.6, 126.7, 134.1, 134.8, 138.5, 181.4; IR (neat,  $\text{cm}^{-1}$ ) 2935, 2178, 1668; HRMS calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}$ : 263.1310. Found: 263.1314.

**3-(1-Decynyl)-1-methylindole-2-carboxaldehyde (3c).** The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 130 mg (88%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J$  = 6.8 Hz, 3H), 1.22-1.40 (m, 8H), 1.45-1.55 (m, 2H), 1.64-1.71 (m, 2H), 2.54 (t,  $J$  = 8.0 Hz, 2H), 4.07 (s, 3H), 7.21 (t,  $J$  = 7.2 Hz, 1H), 7.36 (d,  $J$  = 8.0 Hz, 1H), 7.44 (m, 1H), 7.81 (d,  $J$  = 8.0 Hz, 1H), 10.17 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.1, 18.9, 21.7, 27.8, 27.9, 28.1, 28.2, 30.7, 30.8, 70.2, 97.4, 109.3, 112.2, 120.2, 121.2, 126.6, 126.9, 134.4, 138.5, 181.5; IR (neat,  $\text{cm}^{-1}$ ) 2926, 2232, 1654; HRMS calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}$ : 295.1936. Found: 295.1939.

**3-(Cyclohexylethynyl)-1-methylindole-2-carboxaldehyde (3d).** The reaction mixture was chromatographed using hexanes/EtOAc 15:1 to afford 128 mg (96%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.35-1.50 (m, 3H), 1.50-1.70 (m, 3H), 1.70-1.87 (m, 2H), 1.87-1.98 (m, 2H), 2.75 (m, 1H), 4.04 (s, 3H), 7.20 (m, 1H), 7.33 (m, 1H), 7.42 (m, 1H), 7.80 (dt,  $J$  = 8.4, 0.9 Hz, 1H), 10.25 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.4, 24.6, 28.7, 30.3, 31.3, 69.8, 101.1, 108.9, 111.9, 119.8, 120.8, 126.2, 126.4, 133.9, 138.1, 181.1; IR (neat,  $\text{cm}^{-1}$ ) 2929, 2219, 1669; HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}$ : 265.1467. Found: 265.1472.

**3-(4-Hydroxy-1-butynyl)-1-methylindole-2-carboxaldehyde (3e).** The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford 99 mg (87%) of the indicated compound as a yellow solid: mp 109-110 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.93 (s, 1H), 2.84 (t,  $J$  = 6.4 Hz, 2H), 3.90 (t,  $J$  = 6.4 Hz, 2H), 4.07 (s, 1H), 7.23 (m, 1H), 7.37 (d,  $J$  = 7.8 Hz, 1H), 7.45 (m, 1H), 7.81 (d,  $J$  = 7.8 Hz, 1H), 10.18 (s, 1H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.3, 30.7, 60.2, 72.1, 93.2, 109.4, 111.0, 120.5, 121.0, 126.7, 126.8, 134.6, 138.4, 181.3; IR (neat,  $\text{cm}^{-1}$ ) 3420, 2941, 2233, 1667; HRMS calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}_2$ : 227.0946. Found: 227.0950.

**3-(10-Methoxycarbonyl-1-decynyl)-1-methylindole-2-carboxaldehyde**

**(3f).** The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford 173 mg (98%) of the indicated compound as a yellow solid: mp 53-55 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.45 (m, 6H), 1.45-1.57 (m, 2H), 1.57-1.75 (m, 4H), 2.31 (t,  $J$  = 7.2 Hz, 2H), 2.52 (t,  $J$  = 7.2 Hz, 2H), 3.66 (s, 3H), 4.07 (s, 3H), 7.23 (m, 1H), 7.36 (d,  $J$  = 8.4 Hz, 1H), 7.43 (m, 1H), 7.81 (m, 1H), 10.16 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9, 25.0, 28.8, 28.9, 29.0, 29.1, 29.2, 31.7, 34.1, 51.5, 71.3, 98.4, 110.4, 113.2, 121.3, 122.2, 127.7, 127.9, 135.5, 139.5, 174.4, 182.5; IR (neat,  $\text{cm}^{-1}$ ) 3019, 2929, 2232, 1732, 1664; HRMS calcd for  $\text{C}_{22}\text{H}_{27}\text{NO}_3$ : 353.1991. Found: 353.1998.

**3-(5-Cyano-1-pentynyl)-1-methylindole-2-carboxaldehyde (3g).**

The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 103 mg (82%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.05 (quintet,  $J$  = 7.2 Hz, 2H), 2.62 (t,  $J$  = 7.2 Hz, 2H), 2.77 (t,  $J$  = 6.8 Hz, 2H), 4.08 (s, 3H), 7.24 (t,  $J$  = 6.8 Hz, 1H), 7.38 (d,  $J$  = 8.8 Hz, 1H), 7.46 (t,  $J$  = 6.8 Hz, 1H), 7.78 (d,  $J$  = 8.4 Hz, 1H), 10.16 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.4, 19.1, 24.7, 31.8, 73.3, 94.7, 110.6, 111.8, 119.1, 121.6, 122.0, 127.81, 127.82, 135.6, 139.5, 182.2; IR (neat,  $\text{cm}^{-1}$ ) 2940, 2246, 1668; HRMS calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$ : 250.1106. Found: 250.1110.

**1-Methyl-3-(triethylsilylethynyl)indole-2-carboxaldehyde (3h).**

The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 149 mg (100%) of the indicated compound as a pale yellow solid: mp 55-56 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.75 (m, 6H), 1.10 (m, 9H), 4.08 (s, 3H), 7.24 (m, 1H), 7.37 (d,  $J$  = 8.4 Hz, 1H), 7.45 (m, 1H), 7.82 (dd,  $J$  = 8.0, 0.8 Hz, 1H), 10.22 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.5, 7.7, 31.8, 96.6, 100.4, 110.5, 112.1, 121.7, 122.2, 127.8, 128.0, 136.1, 139.4, 182.4; IR (neat,  $\text{cm}^{-1}$ ) 2953, 2144, 1674; HRMS calcd for  $\text{C}_{18}\text{H}_{23}\text{NOSi}$ : 297.1549. Found: 297.1154.

**3-(1-Hydroxycyclohexylethynyl)-1-methylindole-2-carboxaldehyde (3i).**

The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 141 mg (100%) of the indicated compound as a yellow solid: mp 147-148 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (m, 1H), 1.50-1.90 (m, 7H), 2.10 (m, 2H), 2.55 (s, 1H), 4.03 (s, 1H), 7.22 (t,  $J$  = 7.6 Hz, 1H), 7.33 (d,  $J$  = 8.4 Hz, 1H), 7.43 (t,  $J$  = 7.6 Hz, 1H), 7.78 (d,  $J$  = 8.0 Hz, 1H), 10.16 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.6, 25.2, 31.8, 40.2, 69.6, 75.2, 100.7, 110.5, 111.5, 121.6, 122.1, 127.7, 127.8, 135.5, 139.4, 182.3; IR (neat,  $\text{cm}^{-1}$ ) 3407, 2933, 1655; HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_2$ : 281.1416. Found: 281.1421.

**1-Methoxymethyl-3-(phenylethynyl)indole-2-carboxaldehyde (3j).** The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 138 mg (95%) of the indicated compound as a yellow solid: mp 81-83 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.32 (s, 3H), 6.01 (s, 2H), 7.33 (m, 1H), 7.38-7.45 (m, 3H), 7.51 (m, 1H), 7.57-7.65 (m, 3H), 7.94 (m, 1H), 10.33 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  56.3, 75.1, 80.1, 98.0, 111.9, 114.4, 122.5, 122.7, 123.0, 128.3, 128.7, 128.8, 129.1, 131.9, 135.7, 139.8, 182.3; IR (neat,  $\text{cm}^{-1}$ ) 2212, 1654; HRMS calcd for  $\text{C}_{19}\text{H}_{15}\text{NO}_2$ : 289.1103. Found: 289.1108.

**1-Benzyl-3-(phenylethynyl)indole-2-carboxaldehyde (3k).** The reaction mixture was chromatographed using 12:1 hexanes/EtOAc to afford 149 mg (89%) of the indicated compound as a yellow solid: mp 134-135 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.85 (s, 2H), 7.11 (d,  $J$  = 6.8 Hz, 2H), 7.20-7.30 (m, 4H), 7.38-7.45 (m, 5H), 7.60 (m, 2H), 7.94 (d,  $J$  = 8.0 Hz, 1H), 10.32 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  48.2, 80.2, 97.4, 111.3, 112.8, 122.0, 122.4, 123.0, 126.7, 127.6, 128.0, 128.1, 128.6, 128.7, 131.6, 135.1, 137.3, 139.4, 182.1; IR (neat,  $\text{cm}^{-1}$ ) 3061, 2205, 1667; HRMS calcd for  $\text{C}_{24}\text{H}_{17}\text{NO}$ : 335.1310. Found: 335.1315.

**3-(Phenylethynyl)-1*H*-indole-2-carboxaldehyde (3l).** The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 122 mg (100%) of the indicated compound as a yellow solid: mp 200 °C (decomp);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.27 (m, 1H), 7.37-7.44 (m, 3H), 7.44-7.50 (m, 2H), 7.62 (m, 2H), 7.93 (d,  $J$  = 8.0 Hz, 1H), 9.42 (s, 1H), 10.17 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  80.0, 96.7, 110.1, 112.7, 122.0,

122.3, 122.9, 128.2, 128.6, 128.7, 128.8, 131.7, 136.2, 137.0, 181.1; IR (neat,  $\text{cm}^{-1}$ ) 3278, 1652; HRMS calcd for  $\text{C}_{17}\text{H}_{11}\text{NO}$ : 245.0841. Found: 245.0845.

**1-Methyl-2-(phenylethynyl)indole-3-carboxaldehyde (6a).** The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 121 mg (93%) of the indicated compound as a yellow solid: mp 118-119 °C (lit.<sup>59</sup> mp 120-121 °C);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.3, 77.5, 101.3, 109.8, 119.9, 121.3, 122.3, 123.6, 124.5, 125.1, 128.8, 129.9, 131.9, 132.1, 137.6, 185.2. All other spectral properties are consistent with those reported previously.<sup>59</sup>

**2-(1-Cyclohexenylethynyl)-1-methylindole-3-carboxaldehyde (6b).** The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford 130 mg (98%) of the indicated compound as a yellow solid: mp 84-85 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.60-1.75 (m, 4H), 2.18-2.25 (m, 2H), 2.26-2.33 (m, 2H), 3.81 (s, 3H), 6.43 (m, 1H), 7.27-7.37 (m, 3H), 8.29 (d,  $J = 8.0$  Hz, 1H), 10.15 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.3, 22.1, 26.0, 28.8, 31.1, 75.1, 103.4, 109.6, 119.3, 119.7, 122.1, 123.4, 124.5, 124.8, 133.0, 137.4, 138.9, 185.3; IR (neat,  $\text{cm}^{-1}$ ) 3016, 2935, 2197, 1659; HRMS calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}$ : 263.1310. Found: 263.1314.

**2-(1-Decynyl)-1-methylindole-3-carboxaldehyde (6c).** The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 122 mg (82%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.90 (t,  $J = 3.2$  Hz, 3H), 1.25-1.40 (m, 8H), 1.50 (m, 2H), 1.70 (m, 2H), 2.59 (t,  $J = 7.2$  Hz, 2H), 3.83 (s, 3H), 7.28-7.36 (m, 3H), 8.30 (d,  $J = 8.4$  Hz, 1H), 10.14 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.2, 19.9, 22.7, 28.3, 29.0, 29.1, 31.1, 31.9, 69.3, 103.8, 109.6, 119.5, 122.1, 123.4, 124.4, 124.7, 137.1, 185.4 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 2922, 2232, 1644; HRMS calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}$ : 295.1936. Found: 295.1939.

**2-(Cyclohexylethynyl)-1-methylindole-3-carboxaldehyde (6d).** The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 119 mg (89%) of the indicated compound as a yellow solid: mp 63-65 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.40-1.52 (m, 3H), 1.52-1.71 (m, 3H), 1.71-1.85 (m, 2H), 1.90-2.00 (m, 2H), 2.80 (m, 1H), 3.82 (s, 1H), 7.26-7.36 (m, 3H), 8.29 (m, 1H), 10.15 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$

24.9, 26.0, 30.2, 31.2, 32.4, 69.5, 107.7, 109.8, 119.6, 122.3, 123.5, 124.6, 124.8, 133.6, 137.4, 185.6; IR (neat,  $\text{cm}^{-1}$ ) 2931, 2227, 1654; HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}$ : 265.1467. Found: 265.1472.

**2-(11-Hydroxy-1-undecynyl)-1-methylindole-3-carboxaldehyde (6e).** The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 99 mg (61%) of the indicated compound as a yellow solid: mp 63-65 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.65 (m, 14H), 1.70 (m, 2H), 2.60 (t,  $J = 7.2$  Hz, 2H), 3.65 (t,  $J = 6.8$  Hz, 2H), 3.83 (s, 3H), 7.28-7.37 (m, 3H), 8.30 (d,  $J = 8.4$  Hz, 1H), 10.14 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9, 25.7, 28.3, 28.9, 29.3, 29.4, 31.1, 32.8, 63.1, 69.4, 103.7, 109.6, 119.5, 122.1, 123.4, 124.4, 124.7, 133.3, 137.1, 185.4; IR (neat,  $\text{cm}^{-1}$ ) 3347, 2930, 2233, 1644; HRMS calcd for  $\text{C}_{21}\text{H}_{27}\text{NO}_2$ : 325.2042. Found: 325.2046.

**2-(10-Methoxycarbonyl-1-decynyl)-1-methylindole-3-carboxaldehyde (6f).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 153 mg (86%) of the indicated compound as a yellow solid: mp 42-44 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.40 (m, 6H), 1.42-1.57 (m, 2H), 1.57-1.78 (m, 4H), 2.31 (t,  $J = 7.5$  Hz, 2H), 2.59 (t,  $J = 7.2$  Hz, 2H), 3.66 (s, 3H), 3.83 (s, 3H), 7.27-7.38 (m, 3H), 8.29 (dd,  $J = 8.4, 1.2$  Hz, 1H), 10.14 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.0, 25.1, 28.5, 29.1, 29.30, 29.34, 31.2, 34.3, 51.7, 69.6, 103.8, 109.8, 119.7, 122.3, 123.6, 124.6, 124.9, 133.4, 137.3, 174.5, 185.6 (one  $\text{sp}^3$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 2932, 2231, 1736, 1644; HRMS calcd for  $\text{C}_{22}\text{H}_{27}\text{NO}_3$ : 353.1991. Found: 353.1998.

**1-Methyl-2-(triethylsilylethynyl)indole-3-carboxaldehyde (6g).** The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 140 mg (94%) of the indicated compound as a pale yellow solid: mp 67-69 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.78 (m, 6H), 1.09 (m, 9H), 3.86 (s, 3H), 7.29-7.40 (m, 3H), 8.30 (dd,  $J = 8.4, 1.2$  Hz, 1H), 10.19 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.2, 7.6, 31.1, 93.4, 106.6, 109.8, 120.4, 122.4, 123.6, 124.2, 125.2, 132.0, 137.3, 185.3; IR (neat,  $\text{cm}^{-1}$ ) 2955, 2157, 1661; HRMS calcd for  $\text{C}_{18}\text{H}_{23}\text{NOSi}$ : 297.1549. Found: 297.1154.

**2-(1-Hydroxycyclohexylethynyl)-1-methylindole-3-carboxaldehyde (6h).** The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford

122 mg (87%) of the indicated compound as a yellow solid: mp 155-156 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.40 (m, 1H), 1.51-1.65 (m, 3H), 1.72-1.88 (m, 4H), 2.08-2.15 (m, 2H), 3.30 (br s, 1H), 3.53 (s, 3H), 7.14 (d,  $J$  = 7.6 Hz, 1H), 7.26-7.34 (m, 2H), 8.26 (dd,  $J$  = 6.8, 1.6 Hz, 1H), 10.08 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.4, 25.1, 30.8, 39.7, 69.2, 72.3, 106.2, 109.7, 119.5, 122.1, 123.6, 124.2, 124.9, 132.2, 137.1, 185.5; IR (neat,  $\text{cm}^{-1}$ ) 3390, 2934, 1642; HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_2$ : 281.1416. Found: 281.1421.

**2-(2-Benzofurylethynyl)-1-methylindole-3-carboxaldehyde (6i).** The reaction mixture was chromatographed using hexanes/EtOAc 4:1 to afford 79 mg (78%) of the indicated compound as a yellow solid: mp 147-148 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.93 (s, 3H), 7.21 (s, 1H), 7.28-7.37 (m, 3H), 7.37-7.43 (m, 2H), 7.52 (d,  $J$  = 8.4 Hz, 1H), 7.63 (d,  $J$  = 8.0 Hz, 1H), 8.34 (m, 1H), 10.28 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.5, 83.4, 91.0, 109.8, 111.5, 114.3, 120.8, 121.7, 122.4, 123.8, 124.5, 125.6, 126.7, 127.3, 130.1, 137.0, 137.8, 155.4, 184.9; IR (neat,  $\text{cm}^{-1}$ ) 3062, 2206, 1652; HRMS calcd for  $\text{C}_{20}\text{H}_{13}\text{NO}_2$ : 299.0946. Found: 299.0950.

**1-Methoxymethyl-2-(phenylethynyl)indole-3-carboxaldehyde (6j).** The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 140 mg (97%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.38 (s, 3H), 5.72 (s, 2H), 7.35-7.50 (m, 5H), 7.53 (d,  $J$  = 8.0 Hz, 1H), 7.63 (m, 2H), 8.35 (d,  $J$  = 7.8 Hz, 1H), 10.34 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  56.6, 75.6, 77.2, 101.5, 110.7, 120.9, 121.1, 122.3, 124.1, 124.8, 125.7, 128.8, 130.1, 131.8, 131.9, 137.1, 185.7; IR (neat,  $\text{cm}^{-1}$ ) 2210, 1657; HRMS calcd for  $\text{C}_{19}\text{H}_{15}\text{NO}_2$ : 289.1103. Found: 289.1108.

**1-Benzyl-2-(phenylethynyl)indole-3-carboxaldehyde (6k).** The reaction mixture was chromatographed using 4.5:1 hexanes/EtOAc to afford 122 mg (73%) of the indicated compound as a yellow solid: mp 119-120 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.56 (s, 2H), 7.22-7.35 (m, 8H), 7.35-7.45 (m, 3H), 7.56 (m, 2H), 8.36 (m, 1H), 10.34 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  48.7, 77.6, 101.4, 110.4, 120.2, 121.2, 122.3, 123.6, 124.8, 125.2, 126.9, 128.0, 128.7, 129.0, 129.9, 131.9, 136.0, 137.1, 185.4; IR (neat,  $\text{cm}^{-1}$ ) 3060, 2211, 1655; HRMS calcd for  $\text{C}_{24}\text{H}_{17}\text{NO}$ : 335.1310. Found: 335.1315.



**2-(Phenylethynyl)-1*H*-indole-3-carboxaldehyde (6l).** The reaction mixture was chromatographed using 2.5:1 hexanes/EtOAc to afford 79 mg (64%) of the indicated compound as a yellow solid: mp 171-172 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.30-7.45 (m, 6H), 7.57 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.35 (d, *J* = 7.6 Hz, 1H), 9.08 (s, 1H), 10.33 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 78.2, 98.4, 111.1, 120.8, 121.2, 122.1, 123.6, 124.5, 125.5, 128.7, 129.4, 129.8, 131.9, 135.9, 185.7; IR (neat, cm<sup>-1</sup>) 3198, 1637; HRMS calcd for C<sub>17</sub>H<sub>11</sub>NO: 245.0841. Found: 245.0845.

### Carbolines Prepared

**9-Methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (2a).** The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow solid: mp 135-136 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 3.99 (s, 3H), 7.27-7.38 (m, 2H), 7.45-7.51 (m, 2H), 7.58-7.63 (m, 2H), 8.24 (m, 2H), 8.31 (dt, *J* = 7.8, 0.9 Hz, 1H), 8.64 (d, *J* = 0.9 Hz, 1H), 9.01 (d, *J* = 0.9 Hz, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 29.0, 109.9, 110.8, 119.7, 121.5, 122.0, 126.6, 127.6, 128.5, 128.7, 129.2, 132.0, 136.7, 140.9, 142.5, 146.9; IR (neat, cm<sup>-1</sup>) 3057, 2934; HRMS calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>: 258.1157. Found: 258.1161.

**3-(1-Cyclohexenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (2b).** The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow solid: mp 110-111 °C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 1.65-1.75 (m, 2H), 1.75-1.85 (m, 2H), 2.27 (m, 2H), 2.65 (m, 2H), 3.96 (s, 3H), 6.77 (m, 1H), 7.25 (m, 1H), 7.55-7.62 (m, 2H), 8.15 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.89 (s, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 22.5, 23.2, 25.8, 26.5, 109.8, 119.5, 121.5, 121.8, 124.9, 128.3, 128.8, 131.1, 137.4, 142.4, 149.2 (one sp<sup>3</sup> carbon missing due to overlap); IR (neat, cm<sup>-1</sup>) 3026, 2927; HRMS calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>: 262.1470. Found: 262.1475.

**9-Methyl-3-*n*-octyl-9*H*-pyrido[3,4-*b*]indole (2c).** The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow oil: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 0.87 (m, 3H), 1.25-1.40 (m, 10H),

1.82 (m, 2H), 2.94 (t,  $J = 7.8$  Hz, 2H), 3.97 (s, 3H), 7.23 (m, 1H), 7.59 (dd,  $J = 4.5$ , 0.9 Hz, 2H), 7.91 (d,  $J = 0.9$  Hz, 1H), 8.20 (dt,  $J = 8.1$ , 0.9 Hz, 1H), 8.87 (d,  $J = 0.9$  Hz, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  13.7, 28.4, 28.9, 29.4, 29.5, 29.6, 30.7, 32.0, 38.1, 109.7, 112.6, 119.3, 121.2, 121.8, 128.2, 128.8, 131.5, 135.9, 142.4, 151.4; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2924; HRMS calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_2$ : 294.2096. Found: 294.2101.

**3-Cyclohexyl-9-Methyl-9H-pyrido[3,4-*b*]indole (2d).** The reaction mixture was chromatographed using 20:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford an 87% yield of the indicated compound as a yellow solid: mp 129-130  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.36 (tt,  $J = 12.0$ , 3.2 Hz, 1H), 1.48 (qt,  $J = 12.8$ , 2.4 Hz, 2H), 1.65 (qd,  $J = 12.4$ , 2.8 Hz, 2H), 1.79 (d,  $J = 12.8$  Hz, 1H), 1.91 (d,  $J = 13.2$  Hz, 2H), 2.08 (d,  $J = 11.6$  Hz, 2H), 2.91 (tt,  $J = 12.0$ , 3.2 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.3, 26.9, 29.4, 33.9, 46.5, 109.1, 111.1, 119.3, 121.2, 121.8, 128.2, 129.3, 130.8, 135.8, 142.2, 156.0; IR (neat,  $\text{cm}^{-1}$ ) 2925, 2851; HRMS calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2$ : 264.1627. Found: 264.1632.

**3-(2-Hydroxyethyl)-9-methyl-9H-pyrido[3,4-*b*]indole (2e).** The reaction mixture was chromatographed using acetone to afford a 95% yield of the indicated compound as a white solid: mp 135-136  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  3.13 (t,  $J = 6.4$  Hz, 2H), 3.96 (t,  $J = 6.4$  Hz, 2H), 3.99 (s, 3H), 7.27 (m, 1H), 7.61 (d,  $J = 4.0$  Hz, 2H), 7.96 (s, 1H), 8.22 (d,  $J = 8.0$  Hz, 1H), 8.88 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  29.6, 41.2, 63.1, 110.4, 114.2, 120.1, 121.7, 122.5, 129.1, 129.6, 132.1, 136.8, 143.1, 150.0; IR (neat,  $\text{cm}^{-1}$ ) 3212, 2920; HRMS calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ : 226.1106. Found: 226.1111.

**3-(8-Methoxycarbonyl-1-octyl)-9-methyl-9H-pyrido[3,4-*b*]indole (2f).** The reaction mixture was chromatographed using 20:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford a 95% yield of the indicated compound as a yellow oil, which crystallized upon standing at 0  $^\circ\text{C}$  overnight: mp 67-68  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.40 (m, 8H), 1.60 (m, 2H), 1.80 (m, 2H), 2.29 (t,  $J = 7.5$  Hz, 2H), 2.97 (t,  $J = 7.5$  Hz, 2H), 3.65 (s, 3H), 3.90 (s, 3H), 7.26 (m, 1H), 7.42 (d,  $J = 7.8$  Hz, 1H), 7.59 (dt,  $J = 7.8$ , 0.9 Hz, 1H), 7.80 (br s, 1H), 8.11 (d,  $J = 7.6$  Hz, 1H), 8.79 (br s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.2, 29.37, 29.43, 29.6, 31.0, 34.3, 51.7, 109.3, 119.5, 121.2, 122.0, 128.4, 129.4, 142.4, 174.6 (two  $\text{sp}^3$

carbons are missing due to overlap; two unusual broad peaks are observed at 113.0 and 131.0 ppm, and two  $sp^2$  carbons somehow are missing, even when the noise was very low. Using the 300 and 400 MHz NMR spectrometers or changing the relaxation time of the spectrometers gave similar incomplete spectra); IR (neat,  $cm^{-1}$ ) 2926, 1735; Anal. calcd. for  $C_{22}H_{28}N_2O_2$ : C, 74.97; H, 8.01, N, 7.95. Found: C, 74.45; H, 8.13; N, 7.67; HRMS calcd for  $C_{22}H_{28}N_2O_2$ : 352.2151. Found: 352.2157.

**3-(3-Cyanopropyl)-9-methyl-9H-pyrido[3,4-*b*]indole (2g).** The reaction mixture was chromatographed using 20:1  $CHCl_3/CH_3OH$  to afford an 88% yield of the indicated compound as an off-white solid: mp 187-188 °C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.20 (quintet,  $J = 7.2$  Hz, 2H), 2.38 (t,  $J = 7.2$  Hz, 2H), 3.10 (t,  $J = 7.2$  Hz, 2H), 3.86 (s, 3H), 7.26 (dt,  $J = 8.4, 0.6$  Hz, 1H), 7.41 (d,  $J = 8.4$  Hz, 1H), 7.59 (m, 1H), 7.79 (s, 1H), 8.09 (d,  $J = 7.8$  Hz, 1H), 8.77 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  16.6, 26.0, 29.4, 36.5, 109.3, 113.6, 119.6, 119.9, 120.8, 121.9, 128.5, 129.3, 131.3, 142.2, 148.3; IR (neat,  $cm^{-1}$ ) 3052, 2930, 2243; HRMS calcd for  $C_{16}H_{15}N_3$ : 249.1266. Found: 249.1270.

**9-Methyl-9H-pyrido[3,4-*b*]indole (2h).** The reaction mixture was chromatographed using 10:1  $CHCl_3/CH_3OH$  to afford a 41% yield of the indicated compound as a yellow solid: mp 104-106 °C (lit.<sup>23</sup> mp 106-107 °C);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.84 (s, 3H), 7.26 (t,  $J = 7.6$  Hz, 1H), 7.40 (d,  $J = 8.4$  Hz, 1H), 7.58 (t,  $J = 8.0$  Hz, 1H), 7.90 (br s, 1H), 8.09 (d,  $J = 7.6$  Hz, 1H), 8.46 (br s, 1H), 8.86 (br s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  29.3, 109.2, 119.6, 121.0, 121.8, 128.2, 128.4, 131.8, 138.8, 141.7 (one unusual broad peak is observed at 114.5 ppm and one  $sp^2$  carbon is missing due to overlap); IR (neat,  $cm^{-1}$ ) 3050, 2926; HRMS calcd for  $C_{12}H_{10}N_2$ : 182.0844. Found: 182.0846.

**9-Methoxymethyl-3-phenyl-9H-pyrido[3,4-*b*]indole (2i).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 100% yield of the indicated compound as a white solid: mp 114-115 °C;  $^1H$  NMR (acetone- $d_6$ )  $\delta$  3.30 (s, 3H), 5.90 (s, 2H), 7.34 (q,  $J = 7.6$  Hz, 2H), 7.47 (t,  $J = 7.6$  Hz, 2H), 7.62 (t,  $J = 7.6$  Hz, 1H), 7.76 (d,  $J = 7.6$  Hz, 1H), 8.22 (d,  $J = 8.0$  Hz, 2H), 8.34 (d,  $J = 8.0$  Hz, 1H), 8.68 (s, 1H), 9.14 (s, 1H);  $^{13}C$  NMR (acetone- $d_6$ )  $\delta$  55.5, 74.1, 110.6, 110.8,

120.6, 121.9, 126.5, 127.7, 128.6, 128.7, 130.0, 132.5, 136.2, 140.4, 142.0, 147.8; IR (neat,  $\text{cm}^{-1}$ ) 3062, 1461; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ : 288.1263. Found: 288.1267.

**9-Benzyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (2j).** The reaction mixture was chromatographed using 4.5:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a white solid: mp 145-146 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.53 (s, 2H), 7.17-7.20 (m, 2H), 7.20-7.30 (m, 3H), 7.30-7.58 (m, 6H), 8.09 (dd,  $J = 7.2, 1.5$  Hz, 2H), 8.19 (d,  $J = 7.8$  Hz, 1H), 8.38 (d,  $J = 0.6$  Hz, 1H), 8.87 (d,  $J = 0.6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  47.3, 110.1, 111.6, 120.2, 121.9, 122.2, 126.8, 127.0, 128.0, 128.1, 128.9, 129.0, 129.2, 130.0, 132.0, 136.2, 136.7, 140.7, 142.1, 148.1; IR (neat,  $\text{cm}^{-1}$ ) 3059, 3030, 2936; HRMS calcd for  $\text{C}_{24}\text{H}_{18}\text{N}_2$ : 334.1470. Found: 334.1476.

**5-Methyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (7a).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 92% yield of the indicated compound as a yellow solid: mp 106-107 °C (lit.<sup>59</sup> mp 106-107 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.89 (s, 3H), 7.34 (t,  $J = 7.6$  Hz, 1H), 7.40-7.46 (m, 2H), 7.49-7.56 (m, 3H), 7.69 (s, 1H), 8.11 (d,  $J = 8.0$  Hz, 2H), 8.17 (d,  $J = 8.0$  Hz, 1H), 9.36 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.1, 100.6, 108.9, 118.7, 120.6, 120.7, 121.3, 126.7, 127.3, 128.5, 128.8, 140.6, 141.5, 142.3, 146.1, 153.6; IR (neat,  $\text{cm}^{-1}$ ) 3054, 1594; HRMS calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_2$ : 258.1157. Found: 258.1161.

**3-(1-Cyclohexenyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7b).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a pale yellow solid: mp 99-100 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.72 (m, 2H), 1.85 (m, 2H), 2.32 (m, 2H), 2.63 (m, 2H), 3.78 (s, 3H), 6.85 (m, 1H), 7.25-7.30 (m, 2H), 7.36 (d,  $J = 8.0$  Hz, 1H), 7.48 (dt,  $J = 8.0, 0.9$  Hz, 1H), 8.10 (d,  $J = 8.0$  Hz, 1H), 9.20 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.3, 23.1, 26.1, 26.6, 29.0, 98.8, 108.8, 118.1, 120.4, 120.5, 121.6, 126.3, 128.0, 137.1, 141.4, 141.6, 146.0, 155.4; IR (neat,  $\text{cm}^{-1}$ ) 3050, 2928; HRMS calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_2$ : 262.1470. Found: 262.1475.

**5-Methyl-3-*n*-octyl-5*H*-pyrido[4,3-*b*]indole (7c).** The reaction mixture was chromatographed using 20:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford an 87% yield of the indicated

compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J$  = 6.8 Hz, 3H), 1.20-1.45 (m, 10H), 1.82 (m, 2H), 2.95 (t,  $J$  = 8.0 Hz, 2H), 3.79 (s, 3H), 7.11 (s, 1H), 7.29 (m, 1H), 7.39 (d,  $J$  = 8.0 Hz, 1H), 7.49 (m, 1H), 8.10 (d,  $J$  = 8.0 Hz, 1H), 9.19 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  14.2, 22.7, 29.1, 29.3, 29.6, 30.7, 31.9, 39.2, 102.2, 108.8, 117.8, 120.4, 121.6, 126.3, 141.2, 141.9, 146.1, 158.3; IR (neat,  $\text{cm}^{-1}$ ) 3052, 2924; HRMS calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_2$ : 294.2096. Found: 294.2101.

**3-Cyclohexyl-5-methyl-5*H*-pyrido[4,3-*b*]indole (7d).** The reaction mixture was chromatographed using 20:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford an 83% yield of the indicated compound as a yellow solid: mp 134-135  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.36 (tt,  $J$  = 12.0, 3.2 Hz, 1H), 1.48 (qt,  $J$  = 12.8, 2.4 Hz, 2H), 1.65 (qd,  $J$  = 12.4, 3.2 Hz, 2H), 1.79 (d,  $J$  = 12.4 Hz, 1H), 1.91 (dt,  $J$  = 13.2, 2.8 Hz, 2H), 2.07 (dd,  $J$  = 11.2, 1.6 Hz, 2H), 2.89 (tt,  $J$  = 12.0, 3.2 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.3, 26.8, 29.1, 33.6, 47.2, 100.4, 108.8, 117.9, 120.4, 120.5, 121.6, 126.3, 141.2, 141.8, 146.2, 162.7; IR (neat,  $\text{cm}^{-1}$ ) 2924, 2851; HRMS calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2$ : 264.1627. Found: 264.1632.

**3-(9-Hydroxy-1-nonyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7e).** The reaction mixture was chromatographed using 10:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford a 72% yield of the indicated compound as a white solid: mp 120-121  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28-1.45 (m, 10H), 1.55 (m, 2H), 1.81 (m, 2H), 1.92 (br s, 1H), 2.95 (t,  $J$  = 8.0 Hz, 2H), 3.63 (t,  $J$  = 6.8 Hz, 2H), 3.81 (s, 3H), 7.12 (s, 1H), 7.30 (t,  $J$  = 7.8 Hz, 1H), 7.40 (d,  $J$  = 8.0 Hz, 1H), 7.50 (dt,  $J$  = 8.0, 0.8 Hz, 1H), 8.11 (d,  $J$  = 8.0 Hz, 1H), 9.19 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.8, 29.1, 29.4, 29.50, 29.53, 29.55, 30.6, 32.9, 39.1, 62.9, 102.2, 108.8, 117.8, 120.4, 120.5, 121.5, 126.3, 141.2, 141.8, 146.1, 158.3; IR (neat,  $\text{cm}^{-1}$ ) 3199, 2917; HRMS calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}$ : 324.2202. Found: 324.2206.

**3-(8-Methoxycarbonyl-1-octyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7f).** The reaction mixture was chromatographed using 20:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford an 88% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.45 (m, 8H), 1.61 (m, 2H), 1.82 (m, 2H), 2.29 (t,  $J$  = 7.5 Hz, 2H), 2.94 (t,  $J$  = 7.8 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 7.11 (s, 1H), 7.29 (d,  $J$  = 7.8 Hz, 1H), 7.39 (d,  $J$  = 7.5 Hz, 1H), 7.49 (t,  $J$  = 7.5 Hz, 1H), 8.10 (d,  $J$  = 7.5 Hz, 1H), 9.19 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )

$\delta$  25.2, 29.2, 29.3, 29.4, 29.6, 29.7, 30.8, 34.3, 39.3, 51.7, 102.3, 109.0, 118.0, 120.5, 120.6, 121.7, 126.5, 141.3, 142.1, 146.3, 158.5, 174.6; IR (neat,  $\text{cm}^{-1}$ ) 2927, 1734; HRMS calcd for  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$ : 352.2151. Found: 352.2157.

**5-Methyl-5H-pyrido[4,3-b]indole (7g).** The reaction mixture was chromatographed using 10:1  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to afford a 43% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.80 (s, 3H), 7.28 (br s, 1H), 7.32 (dt,  $J = 7.8, 0.9$  Hz, 1H), 7.42 (d,  $J = 8.1$  Hz, 1H), 7.53 (dt,  $J = 8.1, 0.9$  Hz, 1H), 8.13 (d,  $J = 7.8$  Hz, 1H), 8.60 (br s, 1H), 9.30 (br s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.3, 109.2, 120.8, 120.9, 121.6, 127.1, 141.1, 142.7, 144.9, 145.2, 145.3 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3045, 2930; HRMS calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_2$ : 182.0844. Found: 182.0846.

**3-(2-Benzofuranyl)-5-methyl-5H-pyrido[4,3-b]indole (7h).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 95% yield of the indicated compound as a yellow solid: mp 167-168  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.83 (s, 1H), 7.25 (t,  $J = 7.2$  Hz, 1H), 7.31 (t,  $J = 7.2$  Hz, 2H), 7.38 (d,  $J = 8.0$  Hz, 1H), 7.45 (s, 1H), 7.50 (t,  $J = 8.0$  Hz, 1H), 7.56 (d,  $J = 8.0$  Hz, 1H), 7.64 (d,  $J = 7.8$  Hz, 1H), 7.83 (s, 1H), 8.11 (d,  $J = 7.8$  Hz, 1H), 9.27 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.2, 100.1, 104.1, 109.1, 111.3, 119.0, 120.7, 120.8, 121.4, 121.6, 123.1, 124.8, 126.9, 129.3, 141.6, 142.7, 144.9, 145.5, 155.2, 156.4; IR (neat,  $\text{cm}^{-1}$ ) 3058, 2935; HRMS calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_2$ : 298.1106. Found: 298.1111.

**5-Methoxymethyl-3-phenyl-5H-pyrido[4,3-b]indole (7i).** The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford an 80% yield of the indicated compound as a white solid: mp 101-102  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.31 (s, 3H), 5.68 (s, 2H), 7.35 (m, 1H), 7.41 (m, 1H), 7.48-7.58 (m, 4H), 7.81 (d,  $J = 0.4$  Hz, 1H), 8.09 (m, 2H), 8.14 (d,  $J = 8.0$  Hz, 1H), 9.35 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  56.4, 74.2, 101.3, 109.8, 119.3, 120.8, 121.6, 121.9, 127.1, 127.3, 128.6, 128.8, 140.4, 141.1, 142.6, 146.2, 154.2; IR (neat,  $\text{cm}^{-1}$ ) 3057, 1596; HRMS calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ : 288.1263. Found: 288.1267.

**5-Benzyl-3-phenyl-5H-pyrido[4,3-*b*]indole (7j).** The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a white solid: mp 154-155 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.52 (s, 2H), 7.15 (m, 2H), 7.23-7.30 (m, 3H), 7.32-7.41 (m, 3H), 7.42-7.50 (m, 3H), 7.65 (s, 1H), 8.04 (dd, *J* = 7.2, 1.5 Hz, 2H), 8.18 (d, *J* = 7.5 Hz, 1H), 9.39 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 46.8, 101.2, 109.7, 119.1, 121.0, 121.2, 121.8, 126.6, 127.1, 127.5, 128.1, 128.7, 129.0, 129.2, 136.4, 140.7, 141.4, 142.8, 146.3, 154.1; IR (neat, cm<sup>-1</sup>) 3059, 3030, 2928; HRMS calcd for C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>: 334.1470. Found: 334.1476.

**3-Phenyl-5H-pyrido[4,3-*b*]indole (7k).** The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 49% yield of the indicated compound as a yellow solid: mp 272-273 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.27 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.44-7.55 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 2H), 8.24 (d, *J* = 8.0 Hz, 1H), 9.41 (s, 1H), 11.78 (s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 102.3, 111.5, 112.3, 118.7, 120.1, 120.7, 126.6, 126.7, 128.3, 128.7, 139.9, 140.2, 142.4, 144.9, 151.7; IR (neat, cm<sup>-1</sup>) 3415, 3021; HRMS calcd for C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>: 244.1001. Found: 244.1004.

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### Supporting Information

Copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR for compounds **2b-j**, **3a-l**, **6a-l**, and **7a-k**. This material is included in Appendix B and is also available free of charge via the Internet at <http://pubs.acs.org>.

### References

1. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Tsuji, J., Ed.; Elsevier Press, Lausanne, Switzerland, 1999; pp 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435. For recent reports, see (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (e) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (f) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (g) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412. (h) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (i) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (j) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (k) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (l) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002. (m) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (n) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
2. For recent leading references, see: (a) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (b) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351. (c) Roshchin, A. I.; Bumagin, N. A. *Chem. Heterocycl. Compd.* **1999**, *35*, 171. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101. (e) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (f) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (g) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
3. (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2488. (b) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529.



4. (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (b) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (c) Barluenga, J.; Romanelli, G. P.; Alvarez-García, L. J.; Llorente, I.; González, J. M.; García-Rodríguez, E.; García-Granda, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3136. (d) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578.
5. (a) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (b) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibiho, S. *Heterocycles* **2000**, *53*, 1877. (c) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibiho, S. *J. Org. Chem.* **2001**, *66*, 8793. (d) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477. (e) Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306. (f) Sakamo, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311. (g) Prikhod'ko, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 2383.
6. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.
7. (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193.
8. Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973.
9. (a) Hino, T.; Nakagawa, M. *J. Heterocycl. Chem.* **1994**, *31*, 625. (b) Baker, B. *J. Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 357. (c) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1. (d) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *43*, 6201. (e) Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567. (f) Ohmoto, T.; Koike, K. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 135-170. (g) Matsukura, N.; Kawachi, T.; Morino, K.; Ohgaki, H.; Sugimura, T.; Takayama, S. *Science*, **1981**, *213*, 346. (h) Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles* **1990**, *30*, 271. (i) Gribble, G. W.; In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol.

- 39, Chapter 7. (j) Tan, G. T.; Pezzuto, J. M.; In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: Ft. Collins, CO, 1996; pp 1-119. (k) Nguyen, C. H.; Lavelle, F.; Riou, J.-F.; Bissery, M.-C.; Huel, C.; Bisagni, E. *Anti-Cancer Drug Des.* **1992**, *7*, 235.
10. (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans I* **1999**, 1505. (b) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (c) Engler, T.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444.
11. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.
12. Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359.
13. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds. Perspectives in Organopalladium Chemistry for the XXI Century. Wiley-VCH: Weinheim, 1998: Chapter 5, pp 203-229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
14. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2248.
15. Ethyl propiolate and ethoxyacetylene are prone to polymerization. For examples, see: (a) Gal, Y.-S.; Lee, W.-C.; Choi, S.-K. *Korea Polym. J.* **1997**, *5*, 10. (b) Tabata, M.; Inaba, Y.; Yokota, K.; Nozaki, Y. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *31*, 465. (c) Jacobs, T. L.; Juster, N. *J. Chem. Eng. Data* **1969**, *14*, 125.
16. The base-promoted deacetonation of  $\alpha,\beta$ -acetylenic carbinols has been well studied. For representative examples, see: (a) Veliev, M. G.; Shatirova, M. I.; Chalabiev, C. A.; Mamedov, I. M.; Mustafaev, A. M. *Russ. J. Org. Chem.* **1995**, *31*, 52. (b) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763. (c) Fowler, J. S.; *J. Org. Chem.* **1977**, *42*, 2637. The base-promoted fragmentation of a 1-hydroxycyclohexyl-substituted acetylene is also known. See: (d) Henbest, H. B.; Jones, E. R. H.; Walls, I. M. S. *J. Chem. Soc.* **1949**, 2696.

17. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238
18. The thermal reaction of 1-benzenesulfonyl-3-(trimethylsilylethynyl)indole-2-carboxaldehyde with NH<sub>3</sub> also afforded the corresponding desilylated  $\beta$ -carboline in a low yield (37%). See ref. 5a for details.
19. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C. Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.
20. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. We used ethyl acetate instead of diethyl ether as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in 55% yield.
21. Ranganathan, S.; Maniktala, V.; Kumar, R.; Singh, G. P. *Indian J. Chem. Sec. B* **1984**, *23*, 1197.
22. Erba, E.; Pocar, D.; Valle, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 421.
23. Abramovitch R. A. *Can. J. Chem.* **1960**, *38*, 2273.

### CHAPTER 3. SYNTHESIS OF ANNULATED $\gamma$ -CARBOLINES AND HETEROPOLYCYCLES BY THE PALLADIUM-CATALYZED INTRAMOLECULAR ANNULATION OF ALKYNES

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#### Abstract

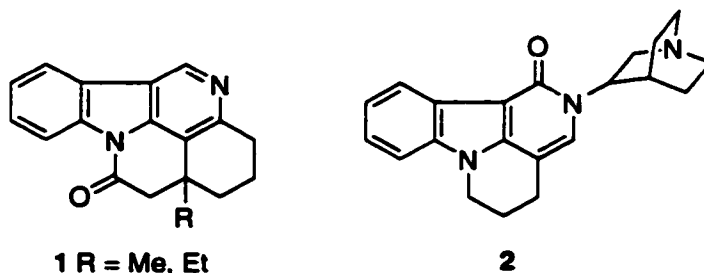
A variety of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various  $\gamma$ -carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields. When the tethered carbon–carbon triple bond is terminal or substituted with a triethylsilyl group, the iminoannulation generates a *tert*-butyl- $\gamma$ -carbolinium salt as the major product. The palladium-catalyzed intramolecular annulations of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, methyl 2-iodo-1*H*-indole-3-carboxylate and 2-iodo-3-phenyl-1*H*-indole containing a phenylpentynyl tether produce the corresponding heteropolycycles in moderate to good yields.

#### Introduction

Annulation processes have proven to be very useful in organic synthesis due to the ease with which a wide variety of complex carbocycles and heterocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology<sup>1</sup> can be effectively employed for the synthesis of indoles,<sup>2</sup> isoindolo[2,1-*a*]indoles,<sup>3</sup> benzofurans,<sup>4</sup> benzopyrans,<sup>4</sup> isocoumarins,<sup>4,5</sup>  $\alpha$ -pyrones,<sup>5,6</sup> indenones,<sup>7</sup> pyridines,<sup>8</sup> isoquinolines,<sup>8</sup> naphthalenes<sup>9</sup>

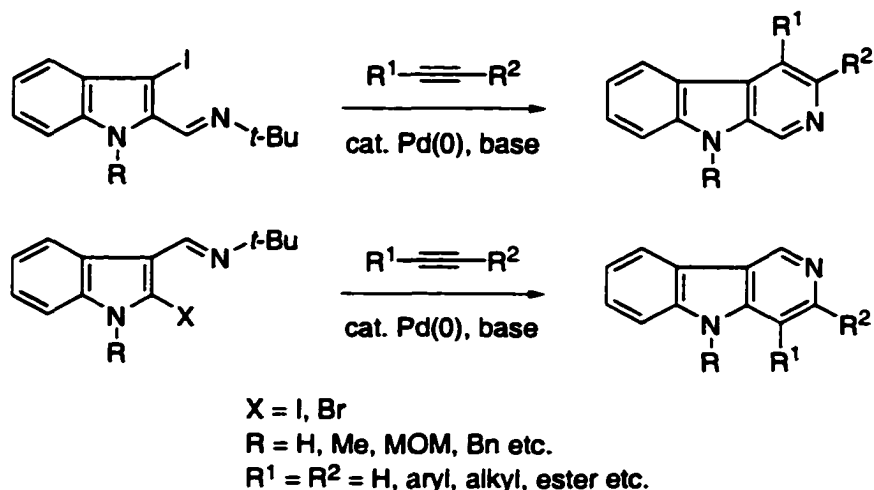
and polycyclic aromatic hydrocarbons.<sup>10</sup> However, intramolecular palladium-catalyzed annulation has not been well explored mainly because of the difficulty of assembling a halide, a carbon-carbon triple bond and other necessary elements into the appropriate positions into a single starting material.<sup>11</sup>

Pyrido[4,3-*b*]-5*H*-indoles, commonly known as  $\gamma$ -carbolines, which are condensed analogues of the ellipticine/olivacine anticancer agents, have been studied extensively because of their potential pharmaceutical importance.<sup>12</sup> However, there are relatively few synthetic studies of  $\gamma$ -carboline derivatives having wide scope and generality,<sup>12,13</sup> and the synthesis of new alkaloid derivatives of  $\gamma$ -carboline with an additional ring fused across the 4- and 5-positions is rare.<sup>14</sup> Two closely related examples of this type of heteropolycyclic system having interesting biological activity are the pentacyclic  $\gamma$ -carboline **1**, which is a cardiovascular agent<sup>15</sup> and the indolonaphthyridone **2**, which acts as a conformationally restricted 5-HT<sub>3</sub> receptor antagonist.<sup>16</sup>

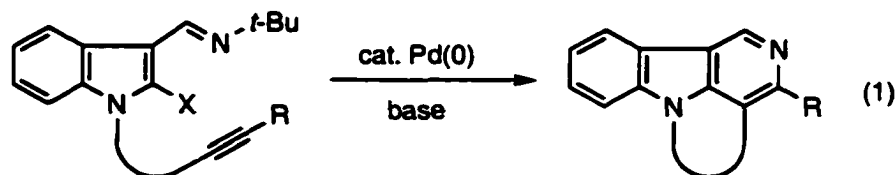


Syntheses of annulated  $\gamma$ -carboline alkaloids have typically employed electrocyclic ring closures of 1-azatrienes,<sup>14c,d</sup> or intramolecular Diels-Alder reactions.<sup>14a,b,e</sup> However, both methods afford the desired  $\gamma$ -carbolines in relatively low yields. Recently, we have developed a general synthesis of 3,4-disubstituted  $\beta$ - and  $\gamma$ -carbolines by the palladium-catalyzed iminoannulation of acetylenes (Scheme 1).<sup>17</sup> While certain  $\beta$ - and  $\gamma$ -carbolines could be prepared in good to excellent

## Scheme 1



yields, the regioselectivity of the reaction was too sensitive to the nature of the alkynes to be of broad applicability.<sup>17</sup> Alternatively, by readily incorporating an alkyne-containing tether onto the indole nitrogen, subsequent palladium-catalyzed intramolecular iminoannulation would enable regioselective construction of two rings in a single step, and provide a well-recognized entropic advantage (eq 1). Our own



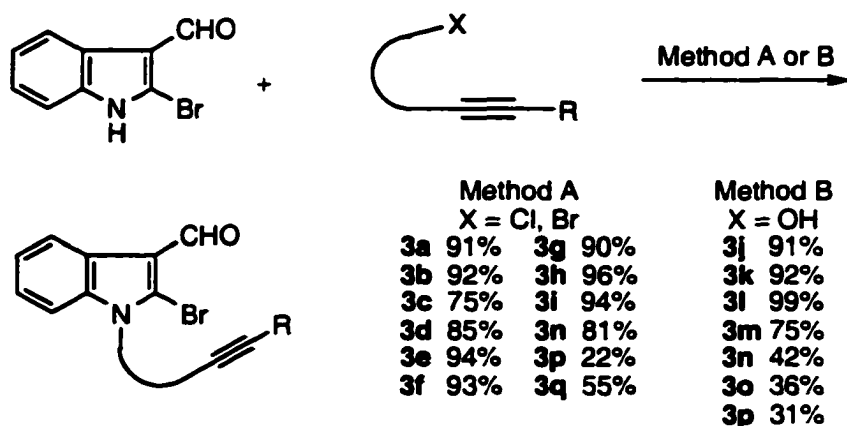
interest in carboline synthesis therefore prompted us to examine the synthesis of a variety of annulated  $\gamma$ -carbolines. A brief communication of this study has been reported previously.<sup>18</sup> Herein, we wish to report the full details of the palladium-catalyzed intramolecular iminoannulation to synthesize annulated  $\gamma$ -carbolines, and extension of this “intramolecular” concept to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

## Results and Discussion

In the early stage of our investigation, we were focused on finding a general, high-yielding method to prepare *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon–carbon triple bond for the

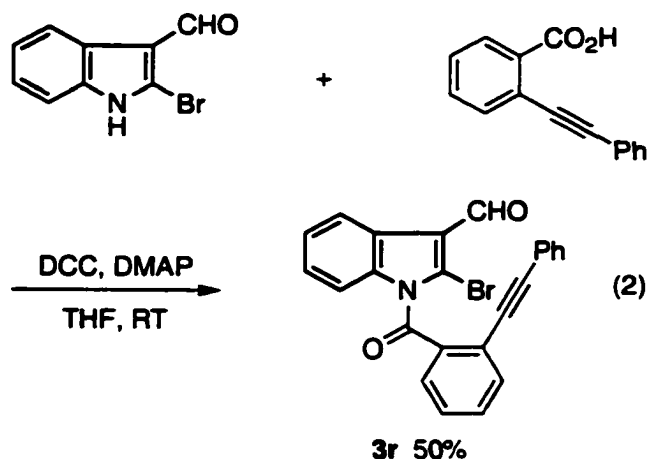
palladium-catalyzed intramolecular iminoannulation. The alkylation and acylation of 1*H*-indole-3-carboxaldehyde to prepare alkyne-tethered indole-3-carboxaldehydes have been reported previously.<sup>14a,b</sup> We anticipated that 2-bromo-1*H*-indole-3-carboxaldehyde<sup>17</sup> would undergo a similar process and were delighted to observe that 2-bromo-1*H*-indole-3-carboxaldehyde reacts readily with the appropriate chlorides or bromides bearing a carbon–carbon triple bond in the presence of NaI and K<sub>2</sub>CO<sub>3</sub> in acetone, affording the desired tethered indoles **3** in excellent yields in most cases (Method A in Scheme 2, see Table 1 and the Experimental Section for details). Relatively low yields were obtained only when the halide contains a conjugated enyne, which might be unstable under the reaction conditions (compare **3c**, **3p** and **3q** with others). An alternative method employing the Mitsunobu reaction<sup>19</sup> of 2-bromo-1*H*-indole-3-carboxaldehyde with sterically unhindered

Scheme 2



alcohols containing a carbon–carbon triple bond has also generated good to excellent yields of the corresponding tethered indoles (Method B in Scheme 2, also see Table 1 and the Experimental Section for details). However, when relatively sterically hindered alcohols were employed, the corresponding Mitsunobu reaction only produced moderate yields of the desired tethered indoles (compare **3n-p** with others). The acylation of 2-bromo-1*H*-indole-3-carboxaldehyde has proven more difficult. After several unsuccessful attempts, we finally managed to couple 2-bromo-1*H*-indole-3-carboxaldehyde with 2-(phenylethynyl)benzoic acid in the

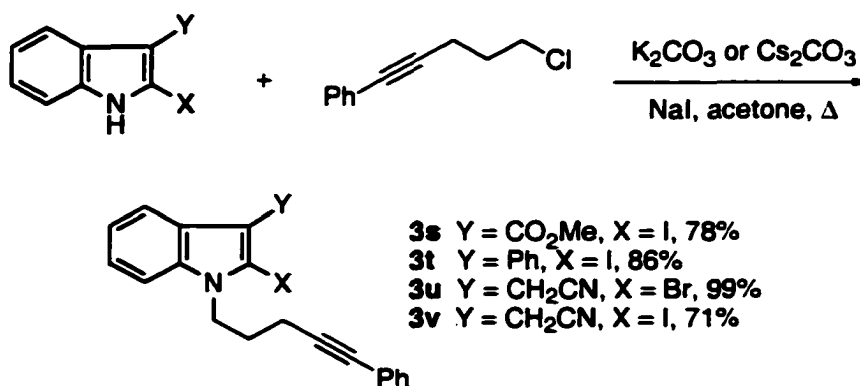
presence of DCC and DMAP,<sup>20</sup> which only afforded a 50% yield of the desired product **3r** (eq 2). Unfortunately, 2-(1-octynyl)benzoic acid and 5-phenylpent-4-ynoic



acid failed to give any significant amount of the products under the same reaction conditions.

Similarly, a phenylpentynyl tether has also been successfully incorporated onto the nitrogen of methyl 2-iodo-1*H*-indole-3-carboxylate, 2-iodo-3-phenyl-1*H*-indole,<sup>21</sup> 2-bromo-1*H*-indole-3-acetonitrile<sup>22</sup> and 2-iodo-1*H*-indole-3-acetonitrile by employing the corresponding 2-haloindoles and 5-chloro-1-phenyl-1-pentyne in the presence of NaI and K<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> in acetone (Scheme 3).

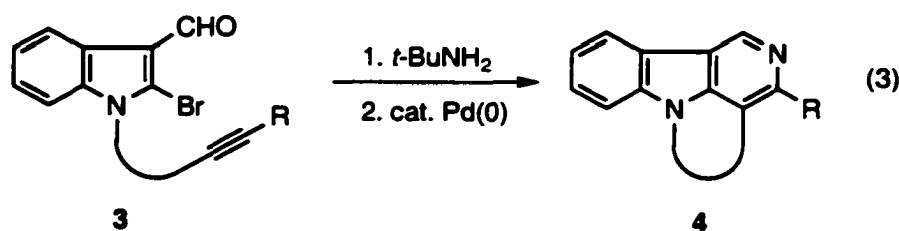
**Scheme 3**



The *tert*-butylimine of indole **3a** was first prepared and employed in the intramolecular palladium-catalyzed iminoannulation under the reaction conditions used in our earlier intermolecular  $\gamma$ -carboline synthesis.<sup>17</sup> Considering that an intramolecular reaction might provide an entropic advantage, we lowered the

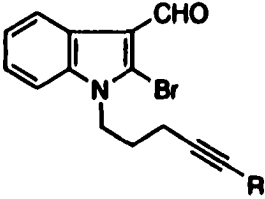
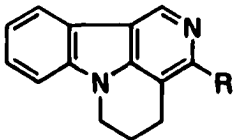
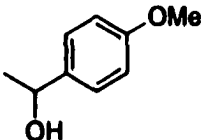
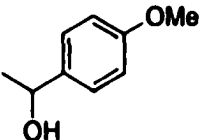
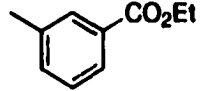
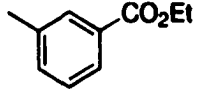
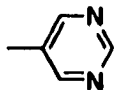
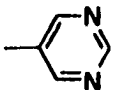


reaction temperature from 125 °C to 100 °C. We were pleased to see that under these reaction conditions, the palladium-catalyzed intramolecular iminoannulation produced a 93% yield of the desired  $\gamma$ -carboline **4a** in only 10 h (Table 1, entry 1). It is noteworthy that the preparation of the *tert*-butylimines from the corresponding aldehydes is essentially quantitative, requiring no further purification and characterization of the starting imines used for the subsequent palladium-catalyzed annulation, as we have observed in our previous work.<sup>17,23</sup> Thus, by employing a two-step protocol, namely imine formation, followed by palladium-catalyzed intramolecular iminoannulation without isolation of the intermediate imine, we have been able to prepare a variety of annulated  $\gamma$ -carbolines and investigate the scope and limitations of this process (eq 3). The results of this investigation are summarized in Table 1.

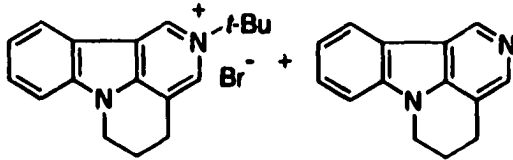
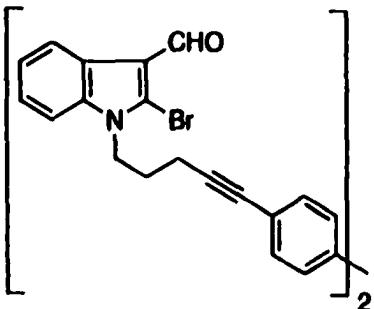
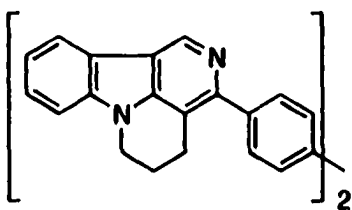
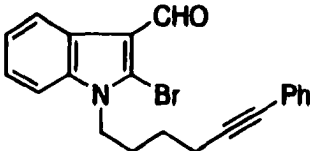
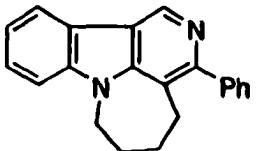


As seen from Table 1, by employing *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes with a trimethylene tether from the indole nitrogen to the carbon-carbon triple bond, the parent isocanthine skeleton<sup>14a</sup> can be readily constructed (entries 1-6). This route allows easy access to a variety of substituted isocanthine derivatives and tolerates various functional groups. For example, tethered indoles **3a-f** containing aryl-, alkyl-, alkenyl-, hydroxy-, ester- and pyrimidyl functionalities all afforded the desired annulation products **4a-f** in excellent yields (entries 1-6). Unfortunately, indole **3g** containing a triethylsilyl group did not generate the desired silyl-substituted isocanthine derivative. Instead, a desilylated  $\gamma$ -carbolinium salt with a *tert*-butyl group on the nitrogen (**4g**) was isolated in a 53% yield, along with a 40% yield of the desilylated isocanthine **4h** (entry 7). Tethered indole **3h** with a terminal carbon-carbon triple bond also afforded the same  $\gamma$ -carbolinium salt **4g** as in the silyl case in a 72% yield, as well as a 10% yield of isocanthine (**4h**) as the minor product

**Table 1. Synthesis of Annulated  $\gamma$ -Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation (eq 3)<sup>a</sup>**

entry	aldehyde	annulation time (h)	product	% yield
	 $\text{R}$		 $\text{R}$	
1	Ph	<b>3a</b> 10	Ph	<b>4a</b> 93
2	$n\text{-C}_6\text{H}_{13}$	<b>3b</b> 24	$n\text{-C}_6\text{H}_{13}$	<b>4b</b> 95
3	( <i>E</i> )-CH=CHPh	<b>3c</b> 10	( <i>E</i> )-CH=CHPh	<b>4c</b> 94
4		<b>3d</b> 18		<b>4d</b> 95
5		<b>3e</b> 12		<b>4e</b> 93
6		<b>3f</b> 40		<b>4f</b> 99

**Table 1. continued**

entry	aldehyde		annulation time (h)	product	% yield
7 <sup>b</sup>	SiEt <sub>3</sub>	3g	18		53 + 40
8	H	3h	40	4g + 4h	72 + 10
9		3i	10		4i 91
10		3j	10		4j 90

**Table 1. continued**

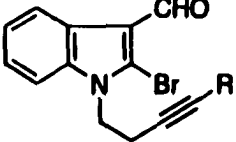
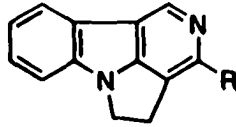
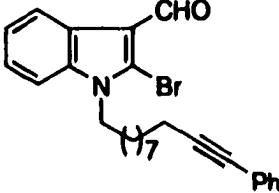
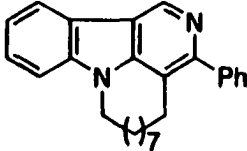
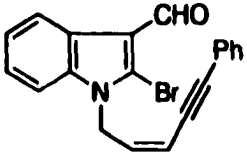
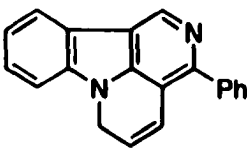
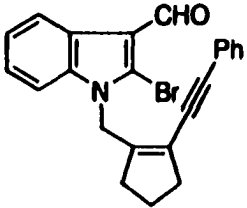
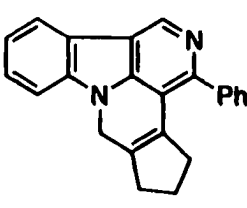
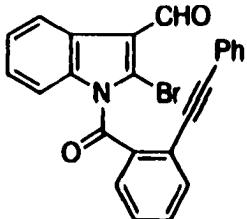
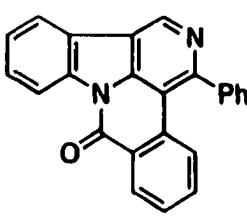
entry	aldehyde	annulation time (h)		product	% yield	
	 <b>R</b>			 <b>R</b>		
11	Ph	<b>3k</b>	24	Ph	<b>4k</b>	84
12	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	<b>3l</b>	12	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	<b>4l</b>	91
13	 <b>R</b>	<b>3m</b>	48	 <b>R</b>	<b>4m</b>	trace

Table 1. continued

entry	aldehyde	annulation time (h)		product		% yield
14	Ph	3n	24	Ph	4n	88
15	<i>n</i> -Bu	3o	20	<i>n</i> -Bu	4o	75
16		3p	18		4p	57
17		3q	14		4q	94
18 <sup>c</sup>		3r	-		4r	-

<sup>a</sup> Representative procedure: the aldehyde (0.25 mmol) and *tert*-butylamine (1 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 8 h. The mixture was cooled, diluted with ether, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated. The residue was dissolved in 5 mL of DMF and transferred to a 4-dram vial containing 5 mol % Pd(OAc)<sub>2</sub>, 10 mol % PPh<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub> (0.25 mmol). The mixture was then flushed with Ar and heated at 100 °C for the indicated time. <sup>b</sup> *n*-Bu<sub>3</sub>N (0.25 mmol) instead of Na<sub>2</sub>CO<sub>3</sub> was used as the base. <sup>c</sup> The amide bond was dissociated during the imine preparation.

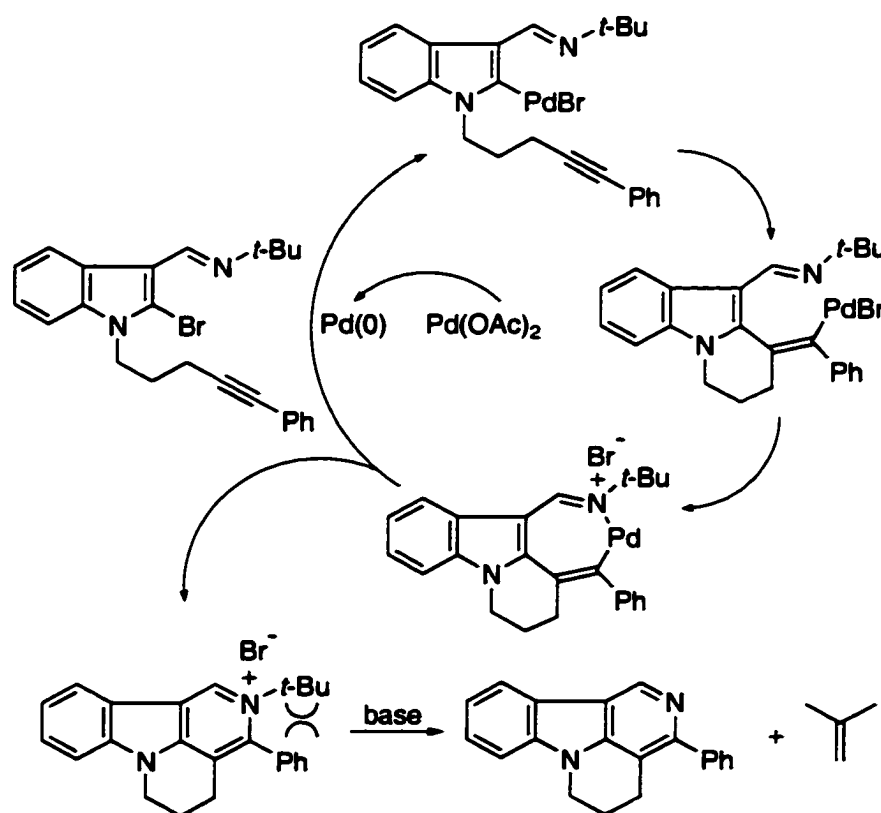
(entry 8, also see the later discussion). As we expected, tethered indole **3i** readily underwent a double intramolecular iminoannulation, generating a complex isocanthine derivative **4i** in an excellent 91% yield (entry 9).

Interestingly, by employing indole **3j** with a tetramethylene tether, we have been able to isolate an annulated  $\gamma$ -carboline **4j** with a seven-membered ring fused to the 4- and 5-positions in a 90% yield (entry 10). We have also been able to obtain annulated  $\gamma$ -carbolines **4k** and **4l** with a five-membered ring fused across the 4- and 5-positions in 84% and 91% yields, by employing indoles **3k** and **3l** with a dimethylene tether, respectively (entries 11 and 12). It is worth noting that ring systems similar to carbolines **4j** and **4k-l** have never been efficiently prepared by either an intramolecular Diels-Alder reaction<sup>24</sup> or the electrocyclization of a 1-azatriene,<sup>14c</sup> since those reactions require significant strain of the tether to achieve the necessary transition-state geometry, especially for the case of a five-five ring juncture. Unfortunately, our attempt to achieve a 12-membered ring fused  $\gamma$ -carboline by employing tethered indole **4m** failed to give any significant amount of the desired product (entry 13). A messy reaction with inseparable multiple products were observed. Presumably because of the entropic disadvantage of forming a 12-membered ring, the competitive intermolecular annulation in this case is significant enough to produce multiple byproducts.

Other types of tethers have also proven to be successful in this intramolecular annulation chemistry. For example, indoles **3n** and **3o** with a tether containing an aryl moiety afforded the desired annulated  $\gamma$ -carbolines **4n** and **4o** in 88% and 75% yields, respectively (entries 14 and 15). Indoles **3p** and **3q** with a tether incorporating an alkene moiety also afforded the desired annulated  $\gamma$ -carbolines **4p** and **4q** in 57% and 94% yields, respectively. The relatively low yield of  $\gamma$ -carboline **4p** may be attributable to the fact that the (*Z*)-enynes moiety in indole **3p** can isomerize<sup>25</sup> or undergo side reactions<sup>11a-c</sup> in the presence of a palladium catalyst. Consistent with this hypothesis is the fact that the more highly substituted enyne **3q** gives an excellent yield.

Unfortunately, indole **3r** having an amide linkage underwent transamidation during imine preparation. Therefore, this palladium-catalyzed intramolecular iminoannulation methodology is limited to those tethered indoles with a  $\text{CH}_2\text{-N}$  bond linkage. Our attempts to oxidize isocanthine **4a** to the corresponding isocanthin-6-one using benzyltriethylammonium permanganate<sup>26</sup> (BTAP), which has been used to oxidize amines to amides<sup>26</sup> and employed to oxidize canthine derivatives to their corresponding canthin-6-ones,<sup>27</sup> also failed to give any significant amount of the desired product.

Scheme 4



We propose a mechanism for this palladium-catalyzed intramolecular iminoannulation chemistry, which is similar to our earlier intermolecular annulation (Scheme 4).<sup>8,17</sup> Specifically, oxidative addition of the indole bromide to Pd(0) produces an organopalladium intermediate, which then intramolecularly adds across

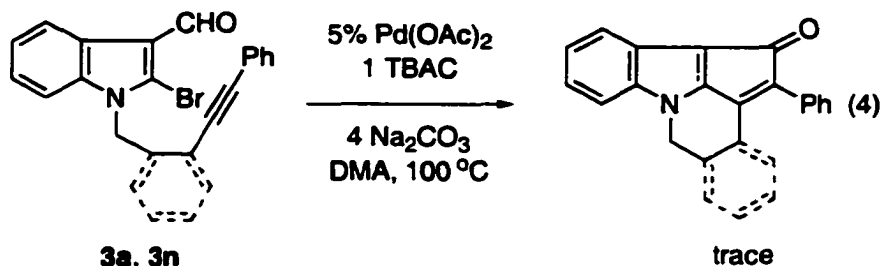
the tethered carbon–carbon triple bond through an exo-dig addition, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic immonium ion salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck,<sup>28</sup> the *tert*-butyl group apparently fragments to relieve the strain resulting from the interaction with the substituent present on the neighboring carbon.

Now it is easy to understand why tethered indole **3h** containing a terminal carbon–carbon produced the *tert*-butylcarbolinium salt **4g** as the major product. In this case, the *tert*-butylcarbolinium salt is unable to fragment the *tert*-butyl group due to the lack of strain between the *tert*-butyl group and the neighboring hydrogen. The observed small amount (10%) of product **4h**, absent of a *tert*-butyl group, presumably arises from thermal fragmentation of the *tert*-butyl group.

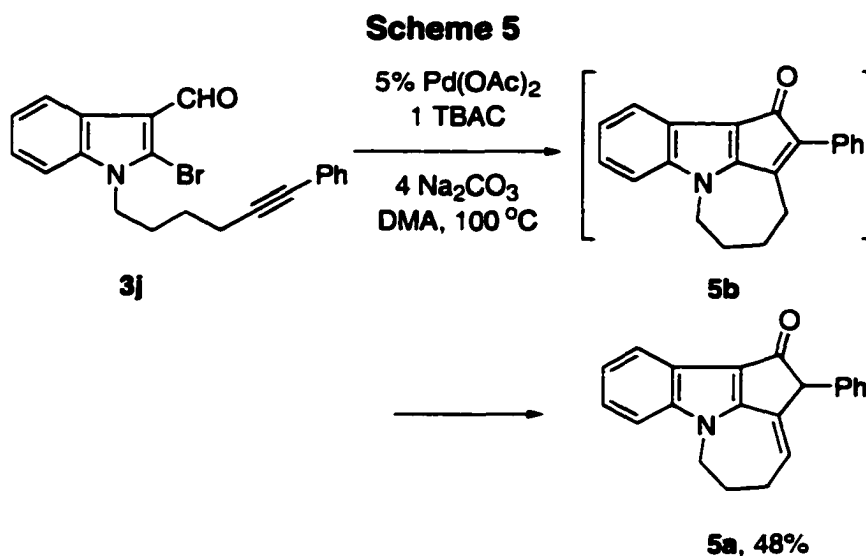
It is also understandable that tethered indole **4g** bearing a triethylsilyl-substituted carbon–carbon triple bond generated a mixture of the desilylated *tert*-butylcarbolinium salt and isocanthine **4h**. In this case, the *tert*-butylcarbolinium intermediate with a *tert*-butyl and a triethylsilyl group on adjacent atoms might undergo either protodesilylation to give the *tert*-butylcarbolinium salt **4g** (53%) without the silyl group or fragmentation of the *tert*-butyl group to give a silyl-substituted isocanthine derivative, which finally protodesilylates under the reaction conditions to give isocanthine **4h** (40%).

Encouraged by the success of our palladium-catalyzed intramolecular iminoannulation, we have also examined several other types of palladium-catalyzed intramolecular annulation. To our disappointment, the intramolecular annulation of aldehydes **3a** and **3n** under the conditions of our earlier indenone synthesis<sup>7</sup> did not generate significant amounts of the desired heterocycles (eq 4), presumably because the desired products having a five-five-six ring juncture are too strained





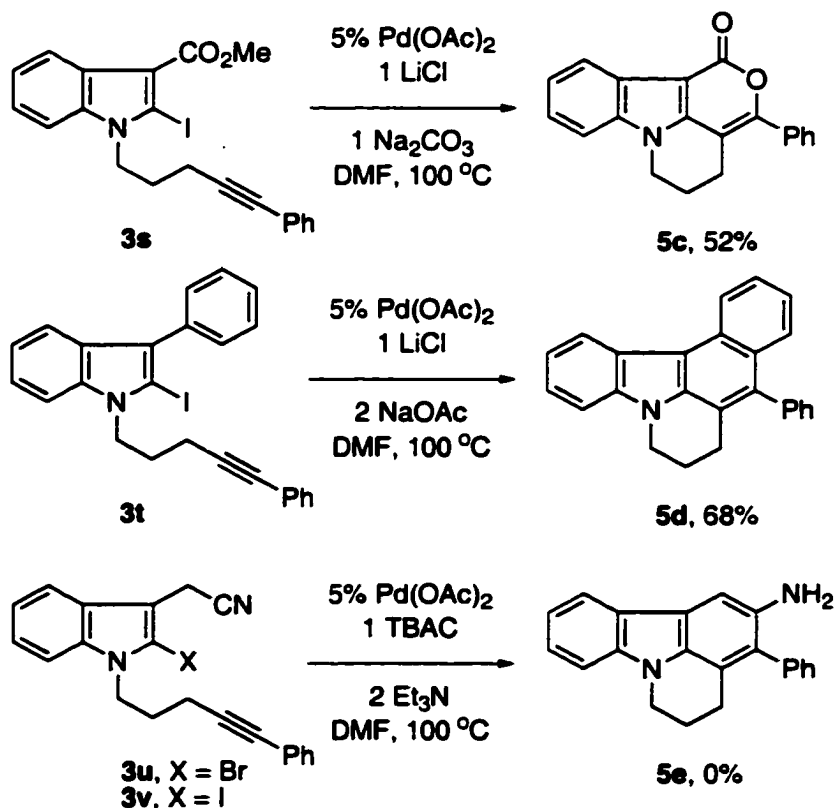
to form or too unstable under the reaction conditions. Interestingly, by simply increasing the length of the linkage, the palladium-catalyzed intramolecular annulation of aldehyde **3j** has generated a 48% yield of heterocycle **5a** with a five-five-seven ring juncture, which apparently arises from tautomerization of the anticipated less stable heterocycle **5b** (Scheme 5). Similar tautomerization has also been previously observed in our indenone synthesis.<sup>7</sup> Unfortunately, the palladium-catalyzed intramolecular annulation of aldehyde **3j** under the conditions of Yamamoto's indenol synthesis<sup>29</sup> did not afford any significant yield of the desired alcohol or the tautomeric ketone.



To our great satisfaction, the intramolecular annulation of alkyne-tethered methyl 2-iodo-1*H*-indole-3-carboxylate **3s** under the conditions of our earlier isocoumarin synthesis<sup>4,5</sup> smoothly produced a 52% yield of the desired heterocycle **5c** (Scheme 6). Equally exciting was the fact that the intramolecular annulation of indole **3t** under the conditions of our earlier phenanthrene synthesis<sup>10</sup> also generated

the desired annulation product **5d** in a 68% yield (Scheme 6). However, neither the 2-bromoindole **3u** nor 2-iodoindole **3v** containing acetonitrile functionality generated any of the desired carbazole **5e** under the conditions of our earlier palladium-catalyzed aminonaphthalene synthesis (Scheme 6).<sup>9b</sup> Messy reactions were observed in both cases. One possible reason is that the 2-haloindoles might be reduced to the corresponding indoles under the reaction conditions, as previously observed in our own laboratory.<sup>30</sup>

### Scheme 6



### Conclusions

In conclusion, a number of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon–carbon triple bond have been prepared, and an efficient synthesis of various annulated  $\gamma$ -carbolines by imination of these aldehydes, followed by palladium-catalyzed intramolecular iminoannulation has been developed. A wide variety of functionalized 2-bromo-1*H*-indole-3-

carboxaldehydes participate in this process to afford the desired  $\gamma$ -carbolines in good to excellent yields. When the tethered carbon–carbon triple bond is terminal or substituted with a silyl group, the iminoannulation generates a *tert*-butyl- $\gamma$ -carbolinium salt as the major product. This chemistry has also been extended to other palladium-catalyzed intramolecular annulations. An *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxylate and 2-iodo-3-phenyl-1*H*-indole containing an alkyne tether have undergone palladium-catalyzed intramolecular annulation, producing the corresponding heteropolycycles in moderate to good yields. However, none of the desired products were observed in the palladium-catalyzed intramolecular annulation of an alkyne-tethered 2-bromo-1*H*-indole-3-acetonitrile or 2-iodo-1*H*-indole-3-acetonitrile.

### Experimental Section

**General.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. Compounds **3a-b**, **3d-f**, **3j**, **3l**, **3n**, **3q**, **4a-b**, **4d-f**, **4j**, **4l**, **4n**, **4q**, and **5a** have been previously reported.<sup>18</sup> 2-Iodo-3-phenyl-1*H*-indole was prepared according to a literature procedure.<sup>21</sup> Following are the preparation and characterization of the starting materials, methyl 2-iodo-1*H*-indole-3-carboxylate, and 2-iodo-1*H*-indole-3-acetonitrile.

**(*E*)-7-Chloro-1-phenylhept-1-en-3-yne.** To a 4-dram vial was added (*E*)- $\beta$ -iodostyrene<sup>31</sup> (0.230 g, 1.0 mmol), CuI (1 mol %), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2 mol %) and Et<sub>3</sub>N (5 mL). The mixture was stirred for 1 min and 5-chloro-1-pentyne (1.2 mmol) was added. The mixture was flushed with Ar and stirred at 60 °C for 3 h. The completion of the reaction was monitored by TLC analysis. The reaction mixture was cooled, diluted with ether and filtered. The solvent was evaporated and the residue was

purified on a silica gel column using 50:1 hexanes/EtOAc to afford 70% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.01 (quintet,  $J = 6.6$  Hz, 2H), 2.56 (dt,  $J = 2.1, 6.6$  Hz, 2H), 3.68 (t,  $J = 6.6$  Hz, 2H), 6.13 (dt,  $J = 16.2, 2.1$  Hz, 1H), 6.88 (d,  $J = 16.2$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 31.8, 44.0, 80.8, 90.2, 108.4, 126.1, 128.4, 128.7, 136.3, 140.6.

**5-Chloro-1-triethylsilyl-1-pentyne.** *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added dropwise to a stirred solution of 5-chloro-1-pentyne (0.513 g, 5.0 mmol) in dry THF (10 mL) at  $-78$  °C under Ar. After 30 min, a solution of triethylsilyl chloride (0.980, 1.3 equiv) in THF (10 mL) was added dropwise. The mixture was warmed to room temperature for 3 h, quenched with satd aq  $\text{NH}_4\text{Cl}$  and extracted with ether. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. The residue was purified using 100:1 hexanes/EtOAc to afford 0.97 g (90%) of the indicated compound as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.57 (q,  $J = 8.0$  Hz, 6H), 0.98 (t,  $J = 8.0$  Hz, 9H), 1.98 (quintet,  $J = 6.4$  Hz, 2H), 2.43 (t,  $J = 6.4$  Hz, 2H), 3.66 (t,  $J = 6.4$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.6, 7.5, 17.3, 31.5, 43.5, 82.8, 106.2.

**4,4'-Bis-(5-chloropent-1-ynyl)biphenyl.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 4,4'-diiodobiphenyl and 5-chloro-1-pentyne (2.4 equiv). The product was purified using 10:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a pale yellow solid: mp  $112$ - $114$  °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.07 (quintet,  $J = 6.8$  Hz, 4H), 2.63 (t,  $J = 6.8$  Hz, 4H), 3.72 (t,  $J = 6.8$  Hz, 4H), 7.45 (d,  $J = 8.0$  Hz, 4H), 7.51 (d,  $J = 8.0$  Hz, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.0, 31.5, 43.8, 81.4, 89.1, 122.9, 126.8, 132.1, 139.7.

**4-Phenylbut-3-yn-1-ol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 3-butyne-1-ol. The product was purified using 2:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.36 (t,  $J = 6.4$  Hz,

1H), 2.67 (t,  $J = 6.4$  Hz, 2H), 3.79 (m, 2H), 7.28 (m, 3H), 7.40 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.8, 61.2, 82.4, 86.5, 123.4, 128.0, 128.3, 131.7.

**11-Phenylundec-10-yn-1-ol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 10-undecyn-1-ol. The product was purified using 3:1 hexanes/EtOAc to afford a 95% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.50 (m, 10H), 1.50-1.65 (m, 5H), 2.41 (t,  $J = 7.2$  Hz, 2H), 3.63 (t,  $J = 7.2$  Hz, 2H), 7.25-7.30 (m, 3H), 7.35-7.42 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.6, 26.0, 29.0, 29.1, 29.3, 29.6, 29.7, 33.0, 63.2, 80.8, 90.7, 124.3, 127.7, 128.4, 131.8.

**2-(Phenylethynyl)benzyl chloride.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl chloride and phenylacetylene. The product was purified using 50:1 hexanes/EtOAc to afford a 100% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.88 (s, 2H), 7.30-7.45 (m, 5H), 7.50-7.62 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  44.8, 86.5, 94.9, 123.0, 123.1, 128.5, 128.7, 128.8, 129.4, 131.7, 132.4, 132.6, 138.9.

**2-(Hex-1-ynyl)benzyl alcohol.** This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl alcohol and 1-hexyne. The product was purified using 5:1 hexanes/EtOAc to afford a 73% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.95 (t,  $J = 7.2$  Hz, 2H), 1.48 (m, 2H), 1.60 (m, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 4.78 (s, 2H), 7.21 (dt,  $J = 1.2, 7.6$  Hz, 1H), 7.27 (dt,  $J = 1.2, 7.6$  Hz, 1H), 7.39 (dt,  $J = 1.2, 7.6$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.7, 19.3, 22.1, 30.9, 64.2, 78.2, 95.5, 122.2, 127.2, 127.4, 128.0, 132.2, 142.4.

**(*Z*)-1-Bromo-5-phenylpent-2-en-4-yne.** To a solution of (*Z*)-5-phenylpent-2-en-4-yn-1-ol<sup>32</sup> (2.2 mmol, 0.348 g) and  $\text{CBr}_4$  (0.948 g, 1.3 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C was added  $\text{PPh}_3$  (1.5 equiv, 0.866 g) portionwise. The mixture was stirred at room temperature for 2 h. The reaction mixture was flushed through a short silica gel column to remove the triphenylphosphine oxide. The solvent was evaporated

and the residue was purified using 25:1 hexanes/EtOAc to afford 0.462 g (95%) of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.27 (d,  $J$  = 8.1 Hz, 2H), 5.85 (d,  $J$  = 10.5 Hz, 1H), 6.20 (m, 1H), 7.35 (m, 3H), 7.47 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.7, 84.3, 97.6, 113.6, 123.0, 128.7, 129.0, 131.9, 137.1.

**Methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate:** *n*-BuLi (2.0 mmol, 2.5 M in hexanes) was added under Ar to a mixture of diisopropylamine (4.0 mmol) and dry THF (20 mL) at  $-78\text{ }^\circ\text{C}$  and the mixture was stirred for 30 min. Methyl 1-phenylsulfonyl-1*H*-indole-3-carboxylate<sup>33</sup> (0.63 g, 2.0 mmol) in dry THF (8 mL) was added to the mixture and stirring was continued at  $-78\text{ }^\circ\text{C}$  for 30 min.  $\text{I}_2$  (1.52 g, 6.0 mmol) in dry THF (10 mL) was added and the mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 2 h. The reaction was quenched by satd aq  $\text{NH}_4\text{Cl}$ , washed with satd aq  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with EtOAc. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated. The residue was purified using 3:1 hexanes/EtOAc to afford 0.756 g (86%) of the indicated compound as a white solid: mp  $138\text{--}140\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.96 (s, 3H), 7.28–7.39 (m, 2H), 7.43–7.50 (m, 2H), 7.60 (tt,  $J$  = 7.5, 1.2 Hz, 1H), 7.92–7.97 (m, 2H), 8.04 (m, 1H), 8.40 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  51.8, 85.5, 115.4, 121.1, 121.6, 124.5, 125.7, 127.5, 128.3, 129.4, 134.6, 138.2, 139.2, 164.0.

**Methyl 2-iodo-1*H*-indole-3-carboxylate:** To a mixture of methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate (0.441 g, 1.0 mmol) in methanol (15 mL) and 1,4-dioxane (5 mL) was added NaOH (0.120 g, 3.0 mmol) and the mixture was heated at  $60\text{ }^\circ\text{C}$  for 18 h. The solvent was evaporated and the residue was purified using 3:1 hexanes/EtOAc to afford 0.181 g (63%) of the indicated compound as a white solid: mp  $159\text{--}160\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.99 (s, 3H), 7.16–7.25 (m, 2H), 7.34–7.40 (m, 1H), 8.12 (m, 1H), 9.02 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  51.4, 86.2, 110.6, 112.3, 121.3, 122.1, 123.4, 126.6, 138.7, 165.0.

**2-iodo-1*H*-indole-3-acetonitrile:** To a mixture of 1*H*-indole-3-acetonitrile (0.781 g, 5.0 mmol) and AgOTs (1.535 g, 5.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added slowly a solution of  $\text{I}_2$  (1.396 g, 5.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) and the mixture was stirred at room temperature for 15 min. The precipitate was filtered and washed with

CH<sub>2</sub>Cl<sub>2</sub>. The solvent was evaporated and the residue was purified using 2:1 hexanes/EtOAc to afford 0.560 g (40%) of the indicated compound as a yellow solid: mp 116-118 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.78 (s, 2H), 7.15-7.22 (m, 2H), 7.34 (dd, *J* = 2.0, 6.4 Hz, 1H), 7.64 (m, 1H), 8.24 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.4, 79.6, 110.7, 111.0, 117.5, 117.7, 121.0, 123.3, 126.6, 138.9.

**General Procedure for the Synthesis of *N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes.** Method A: 2-bromo-1*H*-indole-3-carboxaldehyde<sup>17</sup> (0.5 mmol), the alkynyl halide (0.6 mmol), NaI (0.75 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.75 mmol) were placed in a 4-dram vial and acetone (3 mL) was added. The vial was flushed with Ar and heated in an oil bath at 75 °C for 24 h. The mixture was cooled and diluted with ether (5 mL). The precipitate was removed by filtration and the solvent was evaporated. The residue was purified by chromatography on a silica gel column. Method B: to a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde (0.5 mmol), the alkynyl alcohol (0.6 mmol), and PPh<sub>3</sub> (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added diethyl azodicarboxylate (0.75 mmol) at 0 °C. The resulting mixture was flushed with Ar and stirred at room temperature for 24 h. The mixture was concentrated and the residue was purified by chromatography on a silica gel column.

### ***N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes Prepared**

**2-Bromo-1-[(*E*)-7-phenylhept-6-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3c).** This compound was prepared using (*E*)-7-chloro-1-phenylhept-1-en-3-yne according to Method A. The product was purified using 4:1 hexanes/EtOAc to afford 147 mg (75%) of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.09 (quintet, *J* = 7.2 Hz, 2H), 2.48 (dt, *J* = 2.1, 7.2 Hz, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 6.16 (dt, *J* = 16.2, 2.1 Hz, 1H), 6.90 (d, *J* = 16.2 Hz, 1H), 7.25-7.46 (m, 8H), 8.33 (m, 1H), 10.04 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.4, 28.7, 44.5, 81.5, 90.5, 108.4, 110.1, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 126.4, 128.8, 129.0, 136.5, 137.1, 141.2, 185.6;

IR (neat,  $\text{cm}^{-1}$ ) 3017, 2926, 1654; HRMS calcd for  $\text{C}_{22}\text{H}_{18}\text{BrNO}$ : 391.0572. Found: 391.0579.

**2-Bromo-1-[5-(triethylsilyl)pent-4-ynyl]-1*H*-indole-3-carboxaldehyde (3g).**

This compound was prepared using 5-chloro-1-triethylsilyl-1-pentyne and (*i*-Pr)<sub>2</sub>NEt as the base using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 59-61 °C; <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  0.65 (m, 6H), 1.03 (m, 9H), 2.05 (quintet,  $J = 7.2$  Hz, 2H), 2.39 (t,  $J = 7.2$  Hz, 2H), 4.44 (t,  $J = 7.2$  Hz, 2H), 7.27-7.33 (m, 2H), 7.48 (m, 1H), 8.33 (m, 1H), 10.05 (s, 1H); <sup>13</sup>C NMR ( $\text{CDCl}_3$ )  $\delta$  4.7, 7.8, 17.6, 28.6, 44.4, 57.4, 84.1, 106.2, 110.0, 115.7, 121.5, 123.6, 124.63, 125.6, 125.7, 137.2, 185.6; IR (neat,  $\text{cm}^{-1}$ ) 3056, 2954, 2805, 2172, 1653; HRMS calcd for  $\text{C}_{22}\text{H}_{26}\text{BrNOSi}$ : 403.0967. Found: 403.0974.

**2-Bromo-1-(pent-4-ynyl)-1*H*-indole-3-carboxaldehyde (3h).**

This compound was prepared using 5-chloro-1-pentyne according to method A. The product was purified using 5:1 hexanes/EtOAc to afford a 96% yield of the indicated compound as a yellow solid: mp 94-96 °C; <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  2.05 (quintet,  $J = 7.2$  Hz, 2H), 2.11 (t,  $J = 2.7$  Hz, 1H), 2.31 (dt,  $J = 2.7, 7.2$  Hz, 2H), 4.40 (t,  $J = 7.2$  Hz, 2H), 7.26-7.35 (m, 2H), 7.43 (m, 1H), 8.31 (m, 1H), 10.03 (s, 1H); <sup>13</sup>C NMR ( $\text{CDCl}_3$ )  $\delta$  16.2, 28.4, 44.3, 70.3, 82.7, 110.0, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 137.1, 185.6; IR (neat,  $\text{cm}^{-1}$ ) 3223, 2926, 2806, 1648; HRMS calcd for  $\text{C}_{14}\text{H}_{12}\text{BrNO}$ : 289.0102. Found: 289.0106.

**4,4'-Bis-[5-(2-bromo-3-formylindol-1-yl)pent-1-ynyl]biphenyl (3i).**

This compound was prepared using 4,4'-bis-(5-chloropent-1-ynyl)biphenyl (178 mg, 0.5 mmol), 2-bromo-1*H*-indole-3-carboxaldehyde<sup>17</sup> (268 mg, 1.2 mmol),  $\text{K}_2\text{CO}_3$  (208 mg, 1.5 mmol) and NaI (224 mg, 1.5 mmol) in acetone (6 mL) at 75 °C for 48 h using a modification of method A. The product was purified using 3:2 hexanes/EtOAc to afford 343 mg (94%) of the indicated compound as a yellow solid: mp 135-137 °C; <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  2.17 (m, 4H), 2.56 (t,  $J = 7.2$  Hz, 4H), 4.49 (t,  $J = 7.2$ , 4H), 7.27-7.35 (m, 4H), 7.45-7.50 (m, 6H), 7.51-7.60 (m, 4H), 8.33 (m, 2H), 10.04 (s, 2H); <sup>13</sup>C



NMR (CDCl<sub>3</sub>)  $\delta$  17.1, 28.5, 44.3, 82.0, 89.0, 109.9, 115.5, 121.4, 122.7, 123.5, 124.2, 125.5, 125.6, 126.9, 132.1, 136.9, 139.9, 185.5; IR (neat, cm<sup>-1</sup>) 3022, 2922, 2262, 1653; HRMS calcd for C<sub>40</sub>H<sub>30</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 730.0654. Found: 730.0667.

**2-Bromo-1-(4-phenylbut-3-ynyl)-1*H*-indole-3-carboxaldehyde (3k).** This compound was prepared using 4-phenylbut-3-yn-1-ol according to method B. The product was purified using 3:1 hexanes/EtOAc to afford 161 mg (92%) of the indicated compound as a yellow solid: mp 104-105 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.95 (t, *J* = 7.2 Hz, 2H), 4.53 (t, *J* = 7.2 Hz, 2H), 7.24-7.33 (m, 7H), 7.46 (m, 1H), 8.34 (m, 1H), 10.05 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.6, 44.0, 83.6, 84.8, 110.0, 115.7, 121.4, 122.8, 123.5, 124.2, 125.4, 125.6, 128.2, 128.3, 131.5, 136.8, 185.6; IR (neat, cm<sup>-1</sup>) 3055, 3017, 2807, 2237, 1652; HRMS calcd for C<sub>19</sub>H<sub>14</sub>BrNO: 351.0259. Found: 351.0265.

**2-Bromo-1-(11-phenylundec-10-ynyl)indole-3-carboxaldehyde (3m).** This compound was prepared using 11-phenylundec-10-yn-1-ol according to Method B. The product was purified using 8:1 hexanes/EtOAc to afford a 75% yield of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.25-1.50 (m, 10H), 1.59 (quintet, *J* = 7.2 Hz, 2H), 1.82 (quintet, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 7.22-7.40 (m, 8H), 8.32 (m, 1H), 10.03 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.6, 27.0, 28.9, 29.0, 29.2, 29.4, 29.5, 29.7, 45.7, 80.9, 90.6, 110.1, 115.4, 121.5, 123.5, 124.2, 124.3, 125.6, 125.9, 127.7, 128.4, 131.7, 136.9, 185.7; IR (neat, cm<sup>-1</sup>) 3017, 2930, 2856, 1654; HRMS calcd for C<sub>26</sub>H<sub>28</sub>BrNO: 449.1354. Found: 449.1363.

**2-Bromo-1-[2-(hex-1-ynyl)benzyl]-1*H*-indole-3-carboxaldehyde (3o).** This compound was prepared using 2-(hex-1-ynyl)benzyl alcohol according to method B for 72 h. The product was purified using 7:1 hexanes/EtOAc to afford a 36% yield of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.98 (t, *J* = 7.2 Hz, 2H), 1.54 (sextet, *J* = 7.2 Hz, 2H), 1.67 (quintet, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 6.52 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.18-7.32 (m, 4H), 7.48 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 10.09 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.7, 19.4, 22.2,

30.9, 47.3, 77.8, 97.3, 110.4, 115.7, 121.3, 122.2, 123.6, 124.4, 125.3, 125.4, 126.4, 127.7, 128.3, 132.5, 136.4, 137.2, 185.6; IR (neat,  $\text{cm}^{-1}$ ) 3058, 2956, 2930, 2226, 1661; HRMS calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}$ : 393.0728. Found: 393.0733.

**2-Bromo-1-[(*Z*)-5-phenylpent-2-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3p).** This compound was prepared using (*Z*)-1-bromo-5-phenylpent-2-en-4-yne according to method A for 48 h or (*Z*)-5-phenylpent-2-en-4-yn-1-ol<sup>32</sup> according to method B for 48 h. The product was purified using 5:1 hexanes/EtOAc to afford a 22% yield (method A) or a 31% yield (method B) of the indicated compound as a yellow solid: mp 129-131 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.33 (d,  $J$  = 6.0 Hz, 2H), 5.94 (dd,  $J$  = 6.0, 8.4 Hz, 1H), 5.99 (d,  $J$  = 8.4 Hz, 1H), 7.25-7.31 (m, 2H), 7.31-7.40 (m, 3H), 7.45-7.52 (m, 3H), 8.31 (m, 1H), 10.03 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  44.9, 84.5, 97.2, 110.2, 113.8, 115.7, 121.3, 122.6, 123.5, 124.3, 125.4, 125.6, 128.6, 129.0, 131.6, 134.5, 136.9, 185.5; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2808, 2196, 1654; HRMS calcd for  $\text{C}_{20}\text{H}_{14}\text{BrNO}$ : 363.0259. Found: 363.0265.

**2-Bromo-1-[2-(phenylethynyl)benzoyl]-1*H*-indole-3-carboxaldehyde (3r).** To a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde<sup>17</sup> (86 mg, 0.38 mmol) and 2-(phenylethynyl)benzoic acid<sup>34</sup> (111 mg, 0.5 mmol) in THF (5 mL) was added DMAP (6 mg) and DCC (105 mg), and the mixture was stirred at room temperature for 28 h. The precipitate was filtered and the solvent was evaporated and the residue was purified using 4:1 hexanes/EtOAc to afford a 50% yield of the indicated compound as a yellow solid: mp 136-138 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.69 (d,  $J$  = 8.0 Hz, 2H), 7.09 (t,  $J$  = 7.8 Hz, 2H), 7.20 (m, 1H), 7.32-7.38 (m, 2H), 7.54 (m, 1H), 7.60 (m, 2H), 7.69 (m, 1H), 7.81 (d,  $J$  = 8.0 Hz, 1H), 8.24 (m, 1H), 10.05 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  84.6, 95.6, 113.7, 119.9, 121.1, 121.5, 122.2, 123.5, 125.1, 125.9, 126.1, 128.1, 128.8, 128.9, 130.5, 131.4, 132.9, 133.3, 136.3, 137.1, 168.0, 186.8; IR (neat,  $\text{cm}^{-1}$ ) 3061, 2214, 1699, 1669; HRMS calcd for  $\text{C}_{24}\text{H}_{14}\text{BrNO}_2$ : 427.0208. Found: 427.0213.

## Other Tethered Indoles Prepared

**Methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (3s).** This compound was prepared using methyl 2-iodo-1*H*-indole-3-carboxylate and 5-chloro-1-pentyne at 100 °C using a modification of method A. The product was purified using 4:1 hexanes/EtOAc to afford a 78% yield of the indicated compound as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.08 (quintet, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 3.96 (s, 3H), 4.48 (t, *J* = 7.5 Hz, 2H), 7.18-7.25 (m, 2H), 7.28-7.33 (m, 3H), 7.40-7.50 (m, 3H), 8.12 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.0, 28.6, 47.0, 51.2, 82.1, 88.4, 94.2, 110.2, 111.6, 121.8, 122.0, 123.1, 123.5, 127.5, 128.0, 128.4, 131.6, 138.2, 164.9; IR (neat, cm<sup>-1</sup>) 3053, 2949, 2228, 1697; HRMS calcd for C<sub>21</sub>H<sub>18</sub>INO<sub>2</sub>: 443.0382. Found: 443.0389.

**2-Iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1*H*-indole (3t).** This compound was prepared using 2-iodo-3-phenyl-1*H*-indole,<sup>21</sup> 5-chloro-1-pentyne and Cs<sub>2</sub>CO<sub>3</sub> as the base at 100 °C for 40 h using a modification of method A. The product was purified using 10:1 hexanes/EtOAc to afford an 86% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.13 (quintet, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 4.45 (t, *J* = 7.2 Hz, 2H), 7.08 (t, *J* = 7.6, 1H), 7.21 (t, *J* = 7.6, 1H), 7.28-7.38 (m, 4H), 7.41-7.51 (m, 5H), 7.54-7.61 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.1, 29.1, 46.5, 81.8, 85.8, 88.8, 109.8, 119.2, 120.2, 122.4, 123.4, 123.7, 126.9, 127.9, 128.4, 128.5, 130.1, 131.7, 135.2, 138.1 (one sp<sup>2</sup> carbon missing due to overlap); IR (neat, cm<sup>-1</sup>) 3052, 2933, 2223; HRMS calcd for C<sub>25</sub>H<sub>20</sub>IN: 461.0641. Found: 461.0646.

**2-Bromo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-acetonitrile (3u).** This compound was prepared using 2-bromo-1*H*-indole-3-acetonitrile,<sup>22</sup> 5-chloro-1-pentyne and Cs<sub>2</sub>CO<sub>3</sub> as the base at 75 °C using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.07 (quintet, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 2H), 4.37 (t, *J* = 7.2 Hz, 2H), 7.16-7.32 (m, 5H), 7.38-7.48 (m, 3H), 7.62 (d, *J* = 6.6 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.7, 17.2, 29.1, 44.3, 82.1, 88.7, 103.6, 110.1, 114.0,

117.3, 118.1, 121.0, 123.0, 123.8, 126.3, 128.2, 128.6, 131.8, 136.6; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2929, 2231; HRMS calcd for  $\text{C}_{21}\text{H}_{17}\text{BrN}_2$ : 376.0575. Found: 376.0580.

**2-Iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-acetonitrile (3v).** This compound was prepared using 2-iodo-1*H*-indole-3-acetonitrile, 5-chloro-1-pentyne and  $\text{Cs}_2\text{CO}_3$  as the base at 100 °C for 40 h using a modification of method A. The product was purified using 4:1 hexanes/EtOAc to afford a 71% yield of the indicated compound as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.03 (quintet,  $J = 7.2$  Hz, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 3.77 (s, 2H), 4.34 (t,  $J = 7.2$  Hz, 2H), 7.14-7.22 (m, 2H), 7.25-7.32 (m, 3H), 7.40-7.45 (m, 3H), 7.62 (d,  $J = 7.2$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.9, 17.0, 29.0, 46.6, 82.0, 87.7, 88.6, 109.8, 110.2, 117.3, 117.9, 120.5, 122.8, 123.6, 127.0, 128.0, 128.4, 131.6, 138.1; IR (neat,  $\text{cm}^{-1}$ ) 3057, 2939, 2243; HRMS calcd for  $\text{C}_{21}\text{H}_{17}\text{IN}_2$ : 424.0437. Found: 424.0442.

**General Procedure for the Synthesis of Annulated  $\gamma$ -Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation.** The *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde (0.25 mmol) was placed in a 2-dram vial and *tert*-butylamine (1 mL) was added. The vial was flushed with Ar and carefully sealed. The mixture was heated at 100 °C for 8 h and cooled, diluted with ether, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was evaporated and the residue was dissolved in DMF (5 mL) and transferred to a 4-dram vial containing  $\text{Pd}(\text{OAc})_2$  (5 mol %),  $\text{PPh}_3$  (10 mol %) and  $\text{Na}_2\text{CO}_3$  (0.25 mmol). The mixture was flushed with Ar and heated at 100 °C for the indicated time. The completion of the reaction was established by the observation of palladium black. The mixture (except for entries 4 and 6-8 in Table 1, which produce reasonably water soluble products) was diluted with EtOAc, washed with satd aq  $\text{NH}_4\text{Cl}$  and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the residue was purified by chromatography on a silica gel column. The solvent from the reaction mixtures of entries 4 and 6-8 was directly evaporated and the residue was purified by chromatography on a silica gel column.

### Annulated $\gamma$ -Carbolines Prepared

#### 3-[(*E*)- $\beta$ -Styryl]-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4c).

The mixture was chromatographed using 12:1 CHCl<sub>3</sub>/MeOH to afford 73 mg (94%) of the indicated compound as a yellow solid: mp 131-132 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.35 (quintet, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 4.16 (t, *J* = 7.2 Hz, 2H), 7.24-7.31 (m, 2H), 7.34-7.50 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 15.6 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 9.14 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.3, 22.2, 40.5, 108.8, 114.0, 116.6, 120.4, 121.2, 121.7, 123.9, 126.2, 127.1, 127.9, 128.7, 132.2, 137.5, 140.3, 140.4, 142.9, 146.0; IR (neat, cm<sup>-1</sup>) 3054, 2947, 2865; HRMS calcd for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>: 310.1470. Found: 310.1476.

**2-*tert*-Butyl-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridinium bromide (4g).** The mixture was chromatographed using 4:1 CHCl<sub>3</sub>/MeOH to afford 46 mg (53%) of the indicated compound as a yellow solid: mp >300 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.01 (s, 9H), 2.42 (quintet, *J* = 6.0 Hz, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 4.38 (t, *J* = 6.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 8.78 (d, *J* = 8.0 Hz, 1H), 9.15 (s, 1H), 10.06 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.2, 22.2, 31.1, 41.6, 68.0, 110.2, 118.1, 119.8, 120.9, 123.3, 124.4, 129.4, 132.3, 134.1, 141.7, 143.6; IR (neat, cm<sup>-1</sup>) 3016, 2980; MS *m/z* (rel intensity) 345 (21, M<sup>+</sup>), 209 (100, MH<sup>+</sup>-*t*-Bu-Br). Anal. Calcd for C<sub>18</sub>H<sub>21</sub>BrN<sub>2</sub>: C, 62.62; H, 6.13; N, 8.11. Found: C, 62.16; H, 6.22; N, 8.01.

**5,6-Dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4h).** The mixture was chromatographed using 10:1 CHCl<sub>3</sub>/MeOH to afford 21 mg (40%) of the indicated compound as a yellow solid: mp 268-270 °C (lit.<sup>14c</sup> mp 270 °C). All other spectral properties are identical to those previously reported.<sup>14a,c</sup>

**4,4'-Bis-{5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyrid-3-yl}biphenyl (4i).** The aldehyde (3i, 146 mg, 0.20 mmol), *tert*-butylamine (3 mL) and CHCl<sub>3</sub> (5 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 20 h. The mixture was cooled, diluted with

ether, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. The residue was dissolved in 8 mL of DMF and transferred to a 4-dram vial containing 10 mol %  $\text{Pd}(\text{OAc})_2$ , 20 mol %  $\text{PPh}_3$  and  $\text{Na}_2\text{CO}_3$  (0.40 mmol). The mixture was then flushed with Ar and heated at 100 °C for 10 h. The mixture was chromatographed using 8:1  $\text{CHCl}_3/\text{MeOH}$  on a short silica gel column to afford 103 mg (91%) of the indicated compound as a yellow solid: mp >300 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.32 (quintet,  $J$  = 5.6 Hz, 4H), 3.27 (t,  $J$  = 5.6 Hz, 4H), 4.29 (t,  $J$  = 5.6 Hz, 4H), 7.35 (t,  $J$  = 7.6 Hz, 2H), 7.45 (d,  $J$  = 7.6 Hz, 2H), 7.54 (t,  $J$  = 7.6 Hz, 2H), 7.81 (d,  $J$  = 8.4 Hz, 4H), 7.86 (d,  $J$  = 8.4 Hz, 4H), 8.19 (d,  $J$  = 7.6 Hz, 2H), 9.28 (s, 2H); the  $^{13}\text{C}$  NMR spectrum of compound **4i** was not obtained due to its extremely poor solubility in all the solvents we tried; IR (neat,  $\text{cm}^{-1}$ ) 3050, 2929, 2862; HRMS calcd for  $\text{C}_{40}\text{H}_{30}\text{N}_4$ : 566.2471. Found: 566.2478.

**3-Phenyl-4,5-dihydrobenzo[*b*]pyrido[3,4,5-*gh*]pyrrolizine (4k).** The mixture was chromatographed using 3:2 hexanes/EtOAc to afford 57 mg (84%) of the indicated compound as a yellow solid: mp 171-172 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.06 (t,  $J$  = 7.2 Hz, 2H), 4.53 (t,  $J$  = 7.2 Hz, 2H), 7.28 (m, 1H), 7.37 (t,  $J$  = 8.0 Hz, 2H), 7.42-7.50 (m, 3H), 8.02 (m, 2H), 8.08 (d,  $J$  = 8.0 Hz, 2H), 9.07 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  35.0, 48.7, 110.5, 112.8, 116.5, 120.2, 123.0, 126.0, 127.6, 128.2, 128.7, 139.4, 140.4, 141.0, 146.8, 158.2; IR (neat,  $\text{cm}^{-1}$ ) 3055, 2922, 1559; HRMS calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_2$ : 270.1157. Found: 270.1161.

**1-*n*-Butyl-9*H*-benzo[*c*]indolo[3,2,1-*ij*]-1,6-naphthyridine (4o).** The mixture was chromatographed using 2:3 hexanes/EtOAc to afford 58 mg (75%) of the indicated compound as a yellow solid: mp 129-130 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.03 (t,  $J$  = 7.2 Hz, 3H), 1.58 (m, 2H), 1.90 (m, 2H), 3.29 (t,  $J$  = 8.0 Hz, 2H), 5.40 (s, 2H), 7.30-7.37 (m, 3H), 7.38-7.45 (m, 2H), 7.50 (dt,  $J$  = 0.8, 8.0 Hz, 1H), 8.02 (d,  $J$  = 8.0 Hz, 1H), 8.08 (d,  $J$  = 8.0 Hz, 1H), 8.99 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.1, 23.1, 31.4, 38.1, 45.7, 109.2, 112.2, 116.8, 121.0, 121.2, 122.0, 126.3, 126.7, 127.8, 128.1, 128.2, 129.6, 130.9, 140.3, 140.9, 143.7; IR (neat,  $\text{cm}^{-1}$ ) 3059, 2956, 2870; HRMS calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_2$ : 312.1626. Found: 312.1630.

**3-Phenyl-6*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4p).** The mixture was chromatographed using 1:2 hexanes/EtOAc to afford 40 mg (57%) of the indicated compound as a yellow solid: mp 160-161 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.18 (t, *J* = 2.8 Hz, 2H), 5.97 (dt, *J* = 10.4, 3.2 Hz, 1H), 6.88 (dt, *J* = 10.4, 2.0 Hz, 1H), 7.32-7.44 (m, 3H), 7.46-7.54 (m, 3H), 7.69 (m, 2H), 8.13 (d, *J* = 7.8 Hz, 1H), 9.10 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 44.0, 109.0, 110.9, 116.0, 121.0, 121.4, 121.7, 122.2, 123.1, 126.2, 128.0, 129.6, 139.1, 140.3, 142.5, 142.6, 148.9; IR (neat, cm<sup>-1</sup>) 3056, 2927; HRMS calcd for C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>: 282.1157. Found: 282.1160.

### Heteropolycycles prepared

**3-Phenyl-5,6-dihydro-1*H*,4*H*-benzo[*b*]pyrano[3,4,5-*h**i*]indolizin-1-one (5c).** To a 4-dram vial were added methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (**3s**, 0.25 mmol), Pd(OAc)<sub>2</sub> (5 mol %), Na<sub>2</sub>CO<sub>3</sub> (0.25 mmol), LiCl (0.25 mmol) and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 24 h. The mixture was diluted with EtOAc, washed with satd aq NH<sub>4</sub>Cl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and the residue was purified by chromatography on a silica gel column using 1:1 hexanes/EtOAc to afford 39 mg (52%) of the indicated compound as a white solid: mp 209-210 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.16 (m, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 7.27-7.31 (m, 3H), 7.31-7.46 (m, 3H), 7.65 (m, 2H), 8.15 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 22.1, 22.8, 40.9, 98.2, 103.8, 109.1, 121.4, 122.4, 124.0, 124.3, 128.3 (2), 129.4, 132.3, 138.2, 144.7, 153.4, 159.4; IR (neat, cm<sup>-1</sup>) 3056, 2923, 1702; HRMS calcd for C<sub>20</sub>H<sub>15</sub>NO<sub>2</sub>: 301.1103. Found: 301.1108; Anal. Calcd for C<sub>20</sub>H<sub>15</sub>NO<sub>2</sub>: C, 79.73; H, 5.02; N, 4.65. Found: C, 79.43; H, 4.81; N, 4.41.

**9-Phenyl-7,8-dihydro-6*H*-benzo[*c*]pyrido[1,2,3-*lm*]carbazole (5d).** To a 4-dram vial were added 2-iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1*H*-indole (**3t**, 0.25 mmol), Pd(OAc)<sub>2</sub> (5 mol %), NaOAc (0.50 mmol), LiCl (0.25 mmol) and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 8 h. The mixture was diluted with EtOAc, washed with satd aq NH<sub>4</sub>Cl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>.

The solvent was evaporated and the residue was purified by chromatography on a silica gel column using 10:1 hexanes/EtOAc to afford 56 mg (68%) of the indicated compound as a yellow solid: mp 239-241 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.27 (quintet,  $J = 6.0$  Hz, 2H), 2.89 (t,  $J = 6.0$  Hz, 2H), 4.34 (t,  $J = 6.0$  Hz, 2H), 7.31 (m, 1H), 7.39 (m, 3H), 7.44-7.56 (m, 5H), 7.64 (m, 2H), 8.58 (d,  $J = 8.0$  Hz, 1H), 8.76 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.6, 24.6, 41.1, 108.9, 112.2, 119.7, 120.9, 122.1, 122.4, 123.0, 123.5, 123.7, 125.7, 127.1, 127.7, 128.3, 128.9, 129.0, 130.6, 135.1, 135.5, 138.9, 139.0; IR (neat,  $\text{cm}^{-1}$ ) 3050, 2944; HRMS calcd for  $\text{C}_{25}\text{H}_{18}\text{N}$ : 333.1518. Found: 333.1523. Anal. Calcd for  $\text{C}_{25}\text{H}_{19}\text{N}$ : C, 90.06; H, 5.74; N, 4.20. Found: C, 90.27; H, 5.44; N, 4.17.

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**Supporting Information Available.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **3c**, **3g-l**, **3k**, **3m**, **3o-p**, **3r-v**, **4c**, **4g**, **4k**, **4o-p**, and **5c-d**, and  $^1\text{H}$  NMR spectrum for compound **4i**. This material is included in Appendix C and is also available free of charge via the Internet at <http://pubs.acs.org>.



## References

1. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Ed. J. Tsuji, Elsevier Press, Lausanne, Switzerland, 1999, pp 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.
2. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
3. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.
4. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
5. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
6. Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.
7. Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.
8. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
9. (a) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505. (b) Tian, Q.; Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 339.
10. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.
11. For palladium-catalyzed intramolecular benzoannulations, see: (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653. (b) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (c) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. For other palladium-catalyzed intramolecular annulations, see: (d) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387. (e) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454.
12. (a) Saxton, J. E. in *The Chemistry of Heterocyclic Compounds*; Taylor, E. D., Ed.; Wiley-Intersciences Publication: New York, 1994; Vol. 25. (b) Gribble, G.

- W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, Chapter 7. (c) Tan, G. T.; Pezzuto, J. M. In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: 1996; pp 1-119.
13. (a) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (b) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (c) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587. (d) Hibino, S.; Sugino, E.; Kuwada, T.; Ogura, N.; Sato, K.; Choshi, T. *J. Org. Chem.* **1992**, *57*, 5917. (e) Hibino, S.; Kano, S.; Mochizuki, N.; Sugino, E. *J. Org. Chem.* **1984**, *49*, 5006. (f) Prikhod'ko, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S. *J. Acad. Sci. USSR, Org. Chem.* **1984**, *11*, 2383.
  14. (a) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (b) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111. (c) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. (d) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Heterocycles* **1994**, *37*, 697. (e) Shimoji, Y.; Hashimoto, T.; Furukawa, Y.; Yanagisawa, H. *Heterocycles* **1993**, *36*, 123.
  15. Yanagisawa, H.; Shimoji, Y.; Hashimoto, T. Jpn. Kokai Tokkyo Koho JP 05310738, 1993, Heisei; *Chem. Abstr.* **1994**, *120*, 245056.
  16. Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.
  17. (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318.
  18. Zhang, H.; Larock, R. C. *Org. Lett.* **2002**, *4*, 3035.
  19. For recent reviews of the Mitsunobu reaction, see: (a) Dodge, J. A.; Jones, S. A. *Recent Res. Develop. Org. Chem.* **1997**, *1*, 273. (b) Simon, C.; Hosztafi, S.; Makleit, S. *J. Heterocyclic Chem.* **1997**, *34*, 349. (c) Hughes, D. L. *Org. Prep. Proced. Inter.* **1996**, *28*, 127. (d) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

20. For a similar acylation of 1*H*-indole-3-carboxaldehyde, see: Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55.
21. Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.
22. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
23. (a) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.
24. Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.
25. For a recent review on the palladium-catalyzed isomerization of double bonds, see: Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc.: 2002; Vol. 2, pp 2783-2788.
26. (a) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 68. (b) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 109.
27. Li, J.-H.; Snyder, J. K. *Tetrahedron Lett.* **1994**, *35*, 1485.
28. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.
29. Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.
30. (a) Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428. (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276.
31. Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068.
32. Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558.
33. Wenkert, E.; Moeller, P. D.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.
34. Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023.

## CHAPTER 4. 1,4-PALLADIUM MIGRATION IN THE SUZUKI COUPLING OF $\sigma$ - IODOBIARYLS

A communication submitted to *Angewandte Chemie International Edition*

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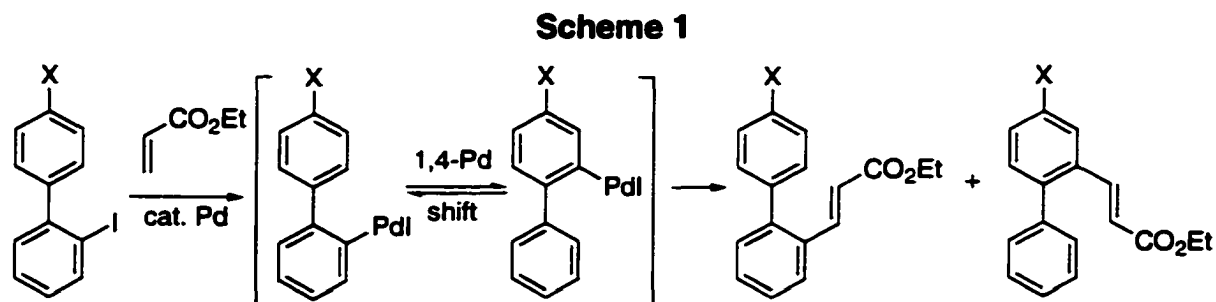
### Abstract

A novel 1,4-palladium migration between the  $\sigma$ - and  $\sigma'$ -positions of biaryls has been observed in the organopalladium intermediates derived from  $\sigma$ -iodobiaryls. The organopalladium intermediates generated by this palladium migration have been trapped by way of a Suzuki coupling reaction with arylboronic acids. The molar ratios of the Suzuki products indicate that palladium has a preference to migrate from a more electron-deficient position to a more electron-rich position in the biaryl.

### Introduction

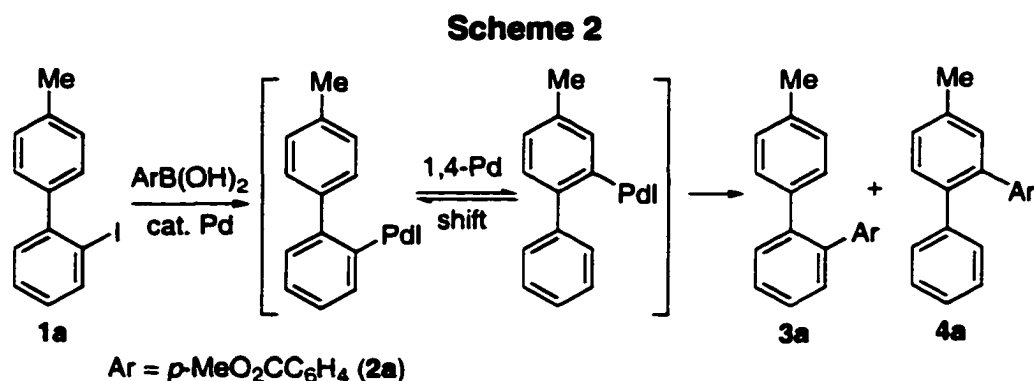
Palladium has been shown to catalyze an extraordinary number of incredibly diverse reactions, making it one of the most useful of all metals for organic synthesis.<sup>1</sup> With the exception of alkene, alkyne and carbon monoxide insertion reactions, the palladium moiety typically stays directly attached to the carbon to which it is originally introduced. However, one of the unique features of palladium is its ability to migrate from one carbon to another.<sup>2</sup> We and others have reported that palladium can migrate through space in Heck coupling reactions.<sup>2e-h</sup> In particular, we have shown that the organopalladium intermediates derived from  $\sigma$ -iodobiaryls lead to a 1,4-palladium migration, and such palladium intermediates can be trapped by Heck reactions with ethyl acrylate (Scheme 1).<sup>2e</sup> However, no palladium migration has been observed previously in Suzuki coupling reactions.<sup>3</sup> Herein, we wish to

report the first examples of palladium migration in Suzuki coupling reactions of *o*-iodobiaryls with arylboronic acids and important mechanistic implications of this chemistry.



## Results and Discussion

In order to obtain a clear idea of what reaction conditions promote palladium migration, we have first studied the Suzuki coupling reaction of 2-iodo-4'-methylbiphenyl (**1a**) and 4-(methoxycarbonyl)phenylboronic acid (**2a**) under various reaction conditions (Scheme 2, Table 1).



The Pd-catalyzed Suzuki coupling of **1a** and **2a** under conditions described by Wright et al<sup>4</sup> produced methyl 4''-methyl-*o*-terphenyl-4-carboxylate (**3a**) exclusively in a 62% yield (entry 1, Table 1). Clearly under these conditions, the coupling reaction proceeds without any palladium migration. The coupling reaction of **1a** and 1 equiv of **2a** was then carried out under our standard migration conditions for the

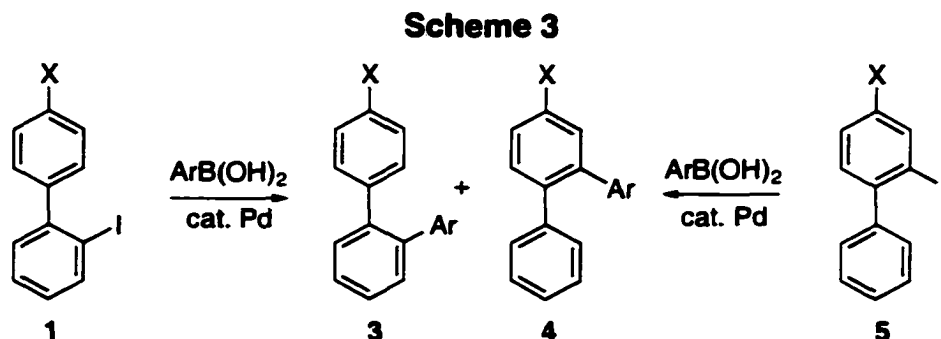
**Table 1. Pd-Catalyzed Reaction of 2-Iodo-4'-methylbiphenyl (1a) and 4-(Methoxycarbonyl)phenylboronic Acid (2a)<sup>a</sup>**

entry	2a equiv	conditions <sup>b</sup>	time (h)	mol ratio <sup>c</sup> 3a:4a	% yield
1	1.2	A	8	100:0	62
2	1.0	B	72	-	trace
3	1.0	B + 20 H <sub>2</sub> O	8	57:43	55
4	1.0	B + 20 H <sub>2</sub> O + 2 PA <sup>d</sup>	24	50:50	57
5	1.4	B + 20 H <sub>2</sub> O + 2 PA <sup>d</sup>	4	51:49	78

<sup>a</sup> All reactions were run using 0.25 mmol of **1a**, 5 mol % Pd(OAc)<sub>2</sub>, and appropriate amounts of boronic acid **2a** and base. <sup>b</sup> Conditions A: 10 mol % PPh<sub>3</sub>, 2.2 equiv of CsF in 1 mL of DME at 90 °C; Conditions B: 5 mol % (Ph<sub>2</sub>P)<sub>2</sub>CH<sub>2</sub> (dppm), 2.0 equiv of CsPiv in 4 mL of DMF at 100 °C. <sup>c</sup> The mol ratio was determined by <sup>1</sup>H NMR spectroscopic analysis. <sup>d</sup> PA = pivalic acid (Me<sub>3</sub>CCO<sub>2</sub>H).

Heck reaction of unsymmetrical *o*-iodobiaryls and ethyl acrylate.<sup>2e</sup> Unfortunately, only a trace amount of coupling products was observed (entry 2). It has been reported that the addition of water facilitates Suzuki coupling reactions.<sup>5</sup> Therefore, we proceeded to carry out the coupling reaction of **1a** with **2a** after adding 20 equiv of H<sub>2</sub>O to the reaction mixture. We were encouraged by obtaining a 57:43 mixture of Suzuki product **3a** and migration product **4a** in a 55% total yield (entry 3). Realizing that, in the presence of base, H<sub>2</sub>O may serve as an OH<sup>-</sup> source, which probably activates the arylboronic acid and facilitates the direct Suzuki coupling prior to Pd migration, we have attempted to control the concentration of OH<sup>-</sup> by buffering the reaction mixture using a combination of 2 equiv of cesium pivalate (CsPiv) and 2 equiv of pivalic acid (PA). To our satisfaction, the reaction of **1a** and **2a** under these buffered conditions produced a 50:50 mixture of **3a** and **4a** in a 57% overall yield (entry 4). An even higher overall yield (78%) of a 51:49 mixture of **3a** and **4a** could be obtained by simply employing 1.4 equiv of arylboronic acid **2a** (entry 5, also entry 1 in Table 2). Thus, we chose this latter set of reaction conditions, described in entry 5, Table 1, which employ 1.4 equiv of boronic acid, 5 mol % Pd(OAc)<sub>2</sub>, 5 mol %

(Ph<sub>2</sub>P)<sub>2</sub>CH<sub>2</sub> (dppm), 2 equiv of CsPiv, 2 equiv of PA and 20 equiv of H<sub>2</sub>O in DMF at 100 °C as our standard migration conditions, for the Suzuki coupling of *o*-iodobiphenyls with arylboronic acids to further explore the scope of this palladium migration process (Scheme 3, Table 2).



**Table 2. Pd-Catalyzed Reaction of *o*-Iodobiphenyls (1 and 5) and Arylboronic Acids (2) under Standard Migration Conditions<sup>a</sup>**

entry	<i>o</i> -iodobiphenyl X =	ArB(OH) <sub>2</sub> Ar =	time (h)	mol ratio <sup>b</sup> 3:4	% yield
1	1a, Me	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (2a)	4	51:49	78
2	5a, Me	(2a)	6	49:51	83
3	1a, Me	Ph (2b)	3	52:48	79
4	5a, Me	(2b)	10	50:50	69
5	1a, Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> (2c)	3	52:48	93
6	5a, Me	(2c)	6	49:51	90
7	1b, MeO	(2a)	4	42:58	85
8	5b, MeO	(2a)	9	39:61	75
9	1c, CO <sub>2</sub> Et	(2a)	10	40:60	84
10	5c, CO <sub>2</sub> Et	(2a)	10	34:66	68

<sup>a</sup> All reactions were run using 0.25 mmol of the *o*-iodobiphenyl, 1.4 equiv of boronic acid, 5 mol % Pd(OAc)<sub>2</sub>, 5 mol % dppm, 2.0 equiv of CsPiv, 2.0 equiv of PA and 20 equiv of H<sub>2</sub>O in 4 mL of DMF at 100 °C. <sup>b</sup> The mol ratio was determined by <sup>1</sup>H NMR spectroscopic analysis.

Interestingly, under our standard migration conditions, 2-iodo-4-methylbiphenyl (**X** = Me, **5a**) and 4-(methoxycarbonyl)phenylboronic acid (**2a**) generated a similar distribution of isomers **3a** and **4a** (49:51) as previously obtained from the reaction of **1a** and **2a** in an overall 83% yield (entry 2, Table 2). Furthermore, similar product distributions have also been observed in the reaction of **1a** and **5a** with phenylboronic acid (**2b**) and 4-methoxyphenylboronic acid (**2c**) (entries 3-6). These results seem to indicate that under our migration conditions, the arylpalladium intermediates generated from either **1a** or **5a** reach apparent equilibrium prior to transmetalation with the boronic acids, since the molar ratios of products **3a-c** to **4a-c** are essentially identical regardless of the electronic properties of the boronic acids **2a-c** employed.

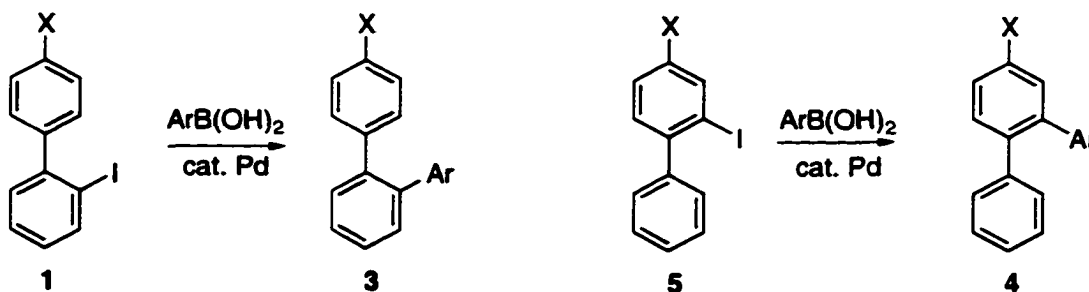
The Pd-catalyzed reaction of methoxy-substituted *o*-iodobiphenyls **1b** and **5b** (**X** = MeO) with boronic acid **2a** under our migration conditions gave more dramatic results (entries 7 and 8). 2'-Iodo-4-methoxybiphenyl (**1b**) generated a 42:58 mixture of **3d** and **4d** in an 85% yield, while 2-iodo-4-methoxybiphenyl (**5b**) afforded **3d** and **4d** in a 75% yield in a very similar 39:61 molar ratio, indicating that palladium has a preference for the more electron-rich aromatic ring. Interestingly, under our standard migration conditions, the reaction of the ester-substituted *o*-iodobiphenyls **1c** and **5c** (**X** = CO<sub>2</sub>Et) with boronic acid **2a** generated similar results to the methoxy-substituted *o*-iodobiphenyls **1b** and **5b** (entries 9 and 10). Thus, **1c** generated a 40:60 mixture of **3e** and **4e** in an 84% yield, while **5c** produced a 34:66 mixture of **3e** and **4e** in a 68% yield. In both cases, palladium seems to prefer to stay attached to the phenyl ring where the ester substituent resides. A preliminary theoretical calculation<sup>6</sup> of the electron densities of the 2- and 2'- positions of ethyl 4-phenylbenzoate indicates that the electron density of the 3-position is higher than that of the 2-position of the phenyl ring, which might explain our results.

It is worth noting that under the reaction conditions described by Wright et al.,<sup>4</sup> all of the Suzuki coupling reactions of *o*-iodobiphenyls **1a-c** and **5a-c** with the boronic acids **2a-c** afforded good to excellent yields (62-98%) of the expected



Suzuki products, without any palladium migration products being observed (Scheme 4, Table 3). Thus, we can simply switch the palladium migration “on” and “off” at will in this biphenyl system by manipulating the reaction conditions.

Scheme 4



**Table 3. Pd-Catalyzed Reaction of *o*-Iodobiphenyls (1 and 5) and Arylboronic Acids (2) under Non-migration Conditions<sup>a</sup>**

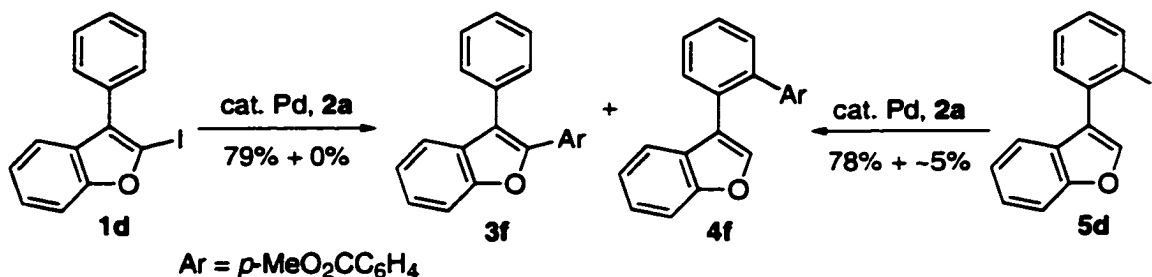
entry	<i>o</i> -iodobiphenyl X =	ArB(OH) <sub>2</sub> Ar =	time (h)	% yield
1	1a, Me	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (2a)	8	62
2	5a, Me	(2a)	12	90
3	1a, Me	Ph (2b)	40	85
4	5a, Me	(2b)	8	93
5	1a, Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> (2c)	18	93
6	5a, Me	(2c)	16	94
7	1b, MeO	(2a)	18	92
8	5b, MeO	(2a)	16	94
9	1c, CO <sub>2</sub> Et	(2a)	16	98
10	5c, CO <sub>2</sub> Et	(2a)	16	97

<sup>a</sup> All reactions were run using 0.25 mmol of the *o*-iodobiphenyl, 1.2 equiv of boronic acid, 5 mol % Pd(OAc)<sub>2</sub>, 10 mol % PPh<sub>3</sub>, 2.2 equiv of CsF in 1 mL of DME at 90 °C.

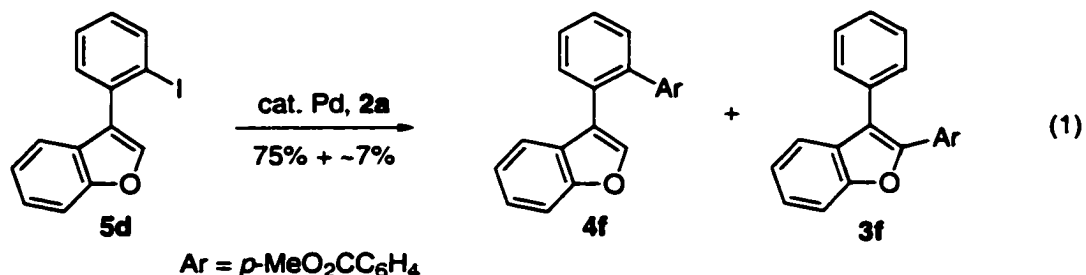
An even more marked effect on the product distribution was observed in the reaction of 2-iodo-3-phenylbenzofuran (1d) with 4-(methoxycarbonyl)phenylboronic

acid (**2a**), which under our standard migration conditions gives exclusively 2-[4-(methoxycarbonyl)phenyl]-3-phenylbenzofuran (**3f**) in a 79% yield in 3 h. Obviously, no palladium migration has occurred in this biaryl system. This is consistent with our Heck migration chemistry<sup>2e</sup> in which the reaction of **1d** with ethyl acrylate shows no palladium migration either. When 3-(2-iodophenyl)benzofuran (**5d**) was allowed to react with boronic acid **2a** under our standard migration conditions, **3f** was produced in a 78% yield in 3 h, along with only ~5% of isomer **4f** (Scheme 5), clearly showing

Scheme 5



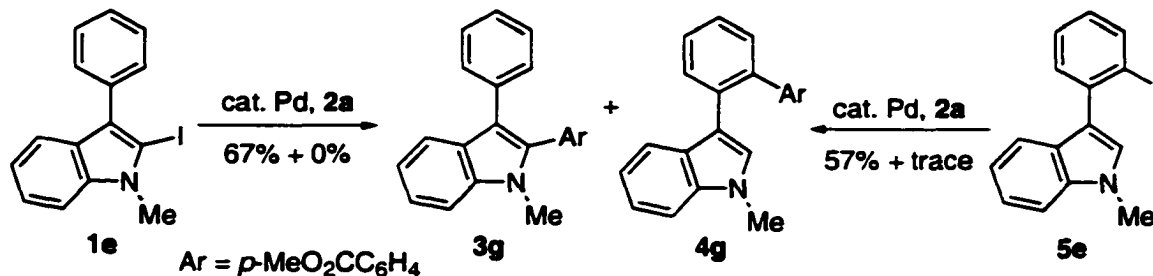
a preference for palladium migration from the phenyl ring to the more electron-rich benzofuran ring. Furthermore, a 75% yield of **4f**, along with only ~7% of benzofuran **3f**, were obtained from **5d** when employing the reaction conditions described by Wright et al (eq 1).<sup>4</sup>



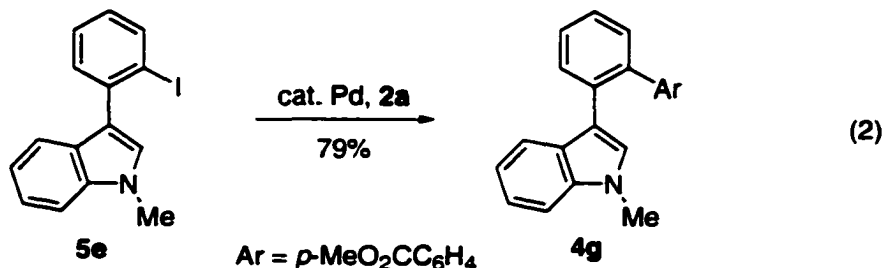
A similar remarkable effect was also observed in the reaction of 2-iodo-1-methyl-3-phenylindole (**1e**) and boronic acid **2a**, which under standard migration conditions gives exclusively the Suzuki product (**3g**) in a 67% yield in 3 h. When 3-(2-iodophenyl)-1-methylindole (**5e**) was allowed to react with boronic acid **2a** under our Pd migration conditions, **3g** was produced in a 57% yield in 6 h, along with a

trace amount of isomer **4g**, again indicating a preference for palladium migration from the phenyl ring to the more electron-rich indole ring (Scheme 6). Moreover, **4g**

**Scheme 6**



can be obtained exclusively in a 79% yield when **5e** is allowed to react with boronic acid **2a** under the non-migration conditions described by Wright et al (eq 2).<sup>4</sup>



## Conclusions

In conclusion, we have observed during Suzuki cross-coupling 1,4-palladium migration in arylpalladium intermediates generated from *o*-iodobiaryls. The choice of reaction conditions is important in turning “on” and “off” the migration. There are important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products. Further investigation of the scope, limitations and mechanism of this palladium migration chemistry is currently underway.

## Experimental Section

**General.** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using

commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. Compounds **1a**,<sup>7</sup> **1b**,<sup>7</sup> **1d**,<sup>2e</sup> **1e**,<sup>7</sup> **5a**,<sup>7</sup> **5b**,<sup>7</sup> and **5d**<sup>7</sup> have been reported before. Compounds **1c**, **5c** and **5e** were prepared as follows.

**Ethyl 4-(2-iodophenyl)benzoate (1c).** To a solution of 4-(2-iodophenyl)benzaldehyde<sup>7</sup> (0.33 g, 1.07 mmol) in ethanol (10 mL) was added activated MnO<sub>2</sub> (1.90 g, 20 equiv), KCN (0.35 g, 5 equiv) and HOAc (0.20 mL, 3 equiv). The mixture was stirred at room temperature for 1 d and filtered. The organic solution was diluted with EtOAc and washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified on a silica gel column using 9:1 hexanes/EtOAc to afford 0.353 g (94%) of the desired compound as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 7.04 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.28 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.37-7.44 (m, 3H), 7.95 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.11 (dt, *J* = 8.4, 1.8 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.7, 61.3, 98.1, 128.5, 129.5 (2), 129.6, 129.9, 130.1, 139.9, 145.9, 148.7, 166.6; IR (neat, cm<sup>-1</sup>) 3042, 2970, 1726; HRMS calcd for C<sub>15</sub>H<sub>13</sub>IO<sub>2</sub>: 351.9960. Found: 351.9966.

**Ethyl 3-iodo-4-phenylbenzoate (5c).** Compound **5c** was prepared from ethyl 4-iodo-3-nitrobenzoate.<sup>8</sup> First, a Suzuki coupling of ethyl 4-iodo-3-nitrobenzoate and NaBPh<sub>4</sub> was carried out as follows. NaBPh<sub>4</sub> (1.69 g, 4.94 mmol), ethyl 4-iodo-3-nitrobenzoate (1.38 g, 4.3 mmol), LiCl (0.182 g, 4.3 mmol), Pd(OAc)<sub>2</sub> (0.048 g, 5 mol %), and PPh<sub>3</sub> (0.113 g, 10 mol %) in DMF (10 mL) were stirred under Ar at 70 °C for 2d. The reaction mixture was diluted with ether and washed with brine. The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to afford a yellow oil, which is presumed to be crude ethyl 3-nitro-4-phenylbenzoate. The crude ethyl 3-nitro-4-phenylbenzoate was dissolved in a mixture of DME/EtOH/AcOH (5:4:1, 50 mL) and SnCl<sub>2</sub> (5.71 g, 30.1 mmol) was added. The resulting mixture was stirred at 60 °C under Ar for 16 h, diluted with ether and washed with 10% aq

$\text{Na}_2\text{CO}_3$ . The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The residue was purified on a silica gel column using 3:1 hexanes/EtOAc to afford 0.93 g (90%) of ethyl 3-amino-4-phenylbenzoate as a yellow oil, which was quickly diazotized and iodinated by the following procedure. To a solution of ethyl 3-amino-4-phenylbenzoate (0.93 g, 3.86 mmol) in DME (10 mL) was added  $\text{H}_2\text{O}$  (8 mL) containing concentrated  $\text{H}_2\text{SO}_4$  (0.7 mL). The reaction mixture was stirred at 0 °C and  $\text{NaNO}_2$  (0.39 g, 5.6 mmol) in  $\text{H}_2\text{O}$  (2 mL) was added dropwise over 30 min. The mixture was stirred for another 20 min at 0 °C and then the mixture was added to  $\text{NaI}$  (3.0 g, 20.0 mmol) in  $\text{H}_2\text{O}$  (7 mL). The mixture was extracted with ether and washed with 10% aq  $\text{Na}_2\text{S}_2\text{O}_3$ . The organic layer was filtered, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was purified on a silica gel column using 7:1 hexanes/EtOAc to afford 1.06 g (78%) of compound **5c** as a white solid: mp 76-77 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.41 (t,  $J$  = 7.2 Hz, 3H), 4.40 (q,  $J$  = 7.2 Hz, 2H), 7.33-7.37 (m, 3H), 7.41-7.45 (m, 3H), 8.04 (dd,  $J$  = 8.0, 1.6 Hz, 1H), 8.61 (d,  $J$  = 1.6 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 61.4, 98.1, 128.2 (2), 129.0, 129.2, 129.9, 130.8, 140.6, 143.4, 150.9, 165.0; IR (neat,  $\text{cm}^{-1}$ ) 2973, 2818, 1722; HRMS calcd for  $\text{C}_{15}\text{H}_{13}\text{IO}_2$ : 351.9960. Found: 351.9966. Anal. calcd for  $\text{C}_{15}\text{H}_{13}\text{IO}_2$ : C, 51.14; H, 3.34. Found: C, 51.16; H, 3.72.

**3-(2-Iodophenyl)-1-methylindole (5e).** Compound **5e** was prepared in two steps from 2-(2-iodophenyl)acetaldehyde.<sup>9</sup> A solution of 2-(2-iodophenyl)acetaldehyde (0.216 g, 0.88 mmol), phenylhydrazine (0.105 g, 0.97 mmol) and methanesulfonic acid (17 mg, 0.18 mmol) in ethanol (5 mL) was stirred at room temperature for 40 min under Ar. Then more methanesulfonic acid (0.152 g, 1.58 mmol) was added and the mixture was stirred at 85 °C for 1.5 d under Ar. The reaction mixture was diluted with ether, washed with satd aq  $\text{NH}_4\text{Cl}$  and the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The residue was purified on a silica gel column using 3:1 hexanes/EtOAc to afford 0.115 g (41%) of 3-(2-iodophenyl)indole as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.99 (m, 1H), 7.13-7.17 (m, 1H), 7.21-7.25 (m, 1H), 7.32-7.47 (m, 4H), 7.53 (d,  $J$  = 8.0 Hz, 1H), 8.00 (dd,  $J$  = 8.0, 0.8

Hz, 1H), 8.18 (br s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  100.9, 111.4, 120.2, 122.5, 123.7, 126.6, 128.1, 128.4, 131.5, 135.7, 139.9, 140.0 (two  $\text{sp}^2$  carbons missing due to overlap). To a suspension of NaH (0.031 g, 1.3 mmol) in DMF (2.0 mL) at 0 °C was added 3-(2-iodophenyl)indole (0.319 g, 1.0 mmol) in DMF (3.0 mL) and the mixture was stirred at room temperature for 30 min. MeI (1.42 g, 10.0 mmol) in DMF (3 mL) was added and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with ether, washed with brine and the organic layer was dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified on a silica gel column using 5:1 hexanes/EtOAc to afford 0.320 g (96%) of compound **5e** as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.84 (s, 3H), 6.97-7.01 (m, 1H), 7.12-7.16 (m, 1H), 7.22-7.28 (m, 2H), 7.35-7.40 (m, 2H), 7.45 (dd,  $J$  = 7.6, 1.6 Hz, 1H), 7.53 (d,  $J$  = 8.0 Hz, 1H), 7.99 (dd,  $J$  = 7.6, 0.8 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.1, 100.8, 109.5, 118.5, 119.7, 120.3, 122.0, 127.0, 128.1, 128.2, 128.4, 131.5, 136.6, 139.9, 140.1; IR (neat,  $\text{cm}^{-1}$ ) 3050, 2922, 1547; HRMS calcd for  $\text{C}_{15}\text{H}_{12}\text{IN}$ : 333.0014. Found: 333.0024.

**General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under the Conditions Described by Wright et al<sup>4</sup> (Non-migration Conditions):** To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.30 mmol, 1.2 equiv),  $\text{Pd}(\text{OAc})_2$  (2.8 mg, 5 mol %),  $\text{PPh}_3$  (6.5 mg, 10 mol %), CsF (84.0 mg, 2.2 equiv) and DME (1.0 mL). The mixture was flushed with Ar and stirred at 90 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled and purified directly by column chromatography on a silica gel column.

**General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under Migration Conditions:** To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.35 mmol, 1.4 equiv),  $\text{Pd}(\text{OAc})_2$  (2.8 mg, 5 mol %),  $(\text{Ph}_2\text{P})_2\text{CH}_2$  (dppm, 4.8 mg, 5 mol %),  $\text{CsO}_2\text{CCMe}_3$  (CsPiv, 117 mg, 2.0 equiv),  $\text{Me}_3\text{CCO}_2\text{H}$  (PA, 51 mg, 2 equiv),  $\text{H}_2\text{O}$  (90 mg, 20 equiv) and DMF (4.0

mL). The mixture was flushed with Ar and stirred at 100 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled, diluted with ether and washed with satd aq NaHCO<sub>3</sub>. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by column chromatography on a silica gel column and the molar ratio of the products was determined by <sup>1</sup>H NMR spectroscopic analysis.

### Suzuki Coupling Products Prepared

**Ethyl 4''-methyl-*o*-terphenyl-4-carboxylate (3a).** This compound was prepared employing **1a** and **2a** under non-migration conditions for 8 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 62% yield of the indicated compound as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.30 (s, 3H), 3.89 (s, 3H), 6.97-7.04 (m, 4H), 7.20-7.23 (m, 2H), 7.40-7.44 (m, 4H), 7.87-7.90 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.3, 52.3, 127.6, 128.3 (2), 129.0, 129.4, 129.9, 130.1, 130.6, 131.0, 136.6, 138.3, 139.7, 140.9, 146.9, 167.4; IR (neat, cm<sup>-1</sup>) 3023, 2918, 1724; HRMS calcd for C<sub>21</sub>H<sub>18</sub>O<sub>2</sub>: 302.1307. Found: 302.1313.

**4-Methyl-*o*-terphenyl (3b).** This compound was prepared employing **1a** and **2b** under non-migration conditions for 40 h. The reaction mixture was chromatographed using 50:1 hexanes/EtOAc to afford an 85% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 74-75 °C (lit.<sup>10</sup> mp 74-75 °C); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.4, 126.7, 127.5, 127.7, 128.1, 128.9, 130.0, 130.2, 130.9, 136.3, 138.8, 140.78, 140.79, 142.0 (one sp<sup>2</sup> carbon missing due to overlap); all other spectral properties are identical to those previously reported.<sup>10,11</sup>

**4-Methoxy-4''-methyl-*o*-terphenyl (3c).** This compound was prepared employing **1a** and **2c** under non-migration conditions for 18 h. The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a colorless oil: <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.2, 55.2, 113.4, 127.2,

127.4, 128.8, 129.8, 130.6, 130.7, 131.0, 134.2, 136.0, 138.8, 140.2, 140.5, 158.3; all other spectral properties are identical to those previously reported.<sup>12</sup>

**Methyl 4''-methoxy-*o*-terphenyl-4-carboxylate (3d).** This compound was prepared employing **1b** and **2a** under non-migration conditions for 18 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 92% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 113-114 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.76 (s, 3H), 3.89 (s, 3H), 6.74 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.41 (m, 4H), 7.90 (d, *J* = 8.4 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 52.1, 55.2, 113.6, 127.3, 128.1, 128.2, 129.3, 129.9, 130.5, 130.7, 131.0, 133.4, 139.4, 140.3, 146.7, 158.5, 167.2; IR (neat, cm<sup>-1</sup>) 3024, 2951, 1721; HRMS calcd for C<sub>21</sub>H<sub>18</sub>O<sub>3</sub>: 318.1256. Found: 318.1261. Anal. calcd for C<sub>21</sub>H<sub>18</sub>O<sub>3</sub>: C, 79.23; H, 5.70. Found: C, 78.90; H, 5.72.

**Ethyl methyl *o*-terphenyl-4,4''-dicarboxylate (3e).** This compound was prepared employing **1c** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 98% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 103-104 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.37 (t, *J* = 7.2 Hz, 3H), 3.89 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 4H), 7.45 (m, 4H), 7.89 (dd, *J* = 2.0, 8.4 Hz, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.4, 52.1, 61.0, 128.28, 128.30, 128.5, 128.8, 129.37, 129.40, 129.87, 129.92, 130.58, 130.60, 139.6, 139.7, 145.8, 145.9, 166.5, 167.0; IR (neat, cm<sup>-1</sup>) 3024, 2985, 1720; HRMS calcd for C<sub>23</sub>H<sub>20</sub>O<sub>4</sub>: 360.1362. Found: 360.1371. Anal. calcd for C<sub>23</sub>H<sub>20</sub>O<sub>4</sub>: C, 76.65; H, 5.59. Found: C, 76.30; H, 5.64.

**2-(4-Methoxycarbonylphenyl)-3-phenylbenzofuran (3f).** This compound was prepared employing **1d** and **2a** under migration conditions for 3 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 79% yield of the indicated compound as a white solid: mp 122-123 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.90 (s, 3H), 7.23-7.27 (m, 1H), 7.34-7.38 (m, 1H), 7.43-7.51 (m, 6H), 7.56-7.58 (m, 1H), 7.71-7.73 (m, 2H), 7.96-7.98 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 52.2, 111.3, 119.6, 120.4,



123.2, 125.5, 126.6, 128.1, 129.2, 129.4, 129.7, 130.1, 132.4, 134.9, 149.3, 154.2, 166.7 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 2917, 2849, 1727; HRMS calcd for  $\text{C}_{22}\text{H}_{16}\text{O}_3$ : 328.1099. Found: 328.1104. Anal. calcd for  $\text{C}_{22}\text{H}_{16}\text{O}_3$ : C, 80.47; H, 4.91. Found: C, 80.12; H, 4.81.

**2-(4-Methoxycarbonylphenyl)-1-methyl-3-phenylindole (3g).** This compound was prepared employing **1e** and **2a** under migration conditions for 3 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 67% yield of the indicated compound as a white solid: mp 122-123 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.71 (s, 3H), 3.94 (s, 3H), 7.19 (m, 2H), 7.27 (m, 4H), 7.32 (t,  $J = 7.2$  Hz, 1H), 7.71 (m, 3H), 7.78 (d,  $J = 8.0$  Hz, 1H), 8.04 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.2, 52.3, 109.8, 116.2, 119.9, 120.5, 122.8, 125.9, 127.0, 128.4, 129.5, 129.7, 130.0, 131.2, 134.8, 136.5, 136.7, 137.8, 166.9; IR (neat,  $\text{cm}^{-1}$ ) 3053, 2950, 1723; HRMS calcd for  $\text{C}_{23}\text{H}_{19}\text{NO}_2$ : 341.1416. Found: 341.1421. Anal. calcd for  $\text{C}_{23}\text{H}_{19}\text{NO}_2$ : C, 80.92; H, 5.61; N, 4.10. Found: C, 80.77; H, 5.53; N, 4.08.

**Methyl 5'-methyl-*o*-terphenyl-4-carboxylate (4a).** This compound was prepared employing **5a** and **2a** under non-migration conditions for 12 h. The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.42 (s, 3H), 3.86 (s, 3H), 7.07 (m, 2H), 7.14-7.26 (m, 7H), 7.32 (m, 1H), 7.86 (dt,  $J = 8.4, 1.8$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.3, 52.3, 126.8, 128.26, 128.34, 129.1, 129.4, 130.1, 130.2, 130.9, 131.4, 137.6, 138.1, 139.6, 141.2, 146.8, 167.3; IR (neat,  $\text{cm}^{-1}$ ) 3025, 2950, 1727; HRMS calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_2$ : 302.1307. Found: 302.1313.

**5'-Methyl-*o*-terphenyl (4b).** This compound was prepared employing **5a** and **2b** under non-migration conditions for 8 h. The reaction mixture was chromatographed using 50:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a colorless oil: all spectral properties are identical to those previously reported.<sup>13</sup>

**4-Methoxy-5'-methyl-*o*-terphenyl (4c).** This compound was prepared employing **5a** and **2c** under non-migration conditions for 16 h. The reaction mixture

was chromatographed using 30:1 hexanes/EtOAc to afford a 94% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 107-108 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.42 (s, 3H), 3.75 (s, 3H), 6.73 (m, 2H), 7.05 (m, 2H), 7.10-7.22 (m, 7H), 7.30 (d,  $J$  = 8.4 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.4, 55.4, 113.6, 126.4, 128.1, 130.2, 130.9, 131.2, 131.6, 134.3, 137.4, 137.9, 140.2, 141.9, 158.5 (one  $\text{sp}^2$  carbon missing due to overlap); IR (neat,  $\text{cm}^{-1}$ ) 3026, 2931, 1516; HRMS calcd for  $\text{C}_{20}\text{H}_{18}\text{O}$ : 274.1358. Found: 274.1362. Anal. calcd for  $\text{C}_{20}\text{H}_{18}\text{O}$ : C, 87.56; H, 6.61. Found: C, 87.62; H, 6.67.

**Methyl 5'-methoxy-*o*-terphenyl-4-carboxylate (4d).** This compound was prepared employing **5b** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 94% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 113-114 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.87 (s, 3H), 3.88 (s, 3H), 6.95-7.01 (m, 2H), 7.02-7.08 (m, 2H), 7.15-7.23 (m, 5H), 7.36 (d,  $J$  = 8.4 Hz, 1H), 7.88 (d,  $J$  = 8.4 Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  52.3, 55.7, 113.8, 116.0, 126.6, 128.2, 128.5, 129.5, 130.09, 130.14, 132.1, 133.6, 140.9, 141.0, 146.6, 159.2, 167.3; IR (neat,  $\text{cm}^{-1}$ ) 3027, 2951, 1723; HRMS calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_3$ : 318.1256. Found: 318.1263. Anal. calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_3$ : C, 79.23; H, 5.70. Found: C, 79.03; H, 5.76.

**Ethyl methyl *o*-terphenyl-5',4-dicarboxylate (4e).** This compound was prepared employing **5c** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford a 97% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 105-106 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.41 (t,  $J$  = 7.2 Hz, 3H), 3.89 (s, 3H), 4.42 (q,  $J$  = 7.2 Hz, 2H), 7.11 (m, 2H), 7.20-7.24 (m, 5H), 7.51 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.4 Hz, 2H), 8.10 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.6, 52.3, 61.4, 127.6, 128.4, 128.8, 129.3, 129.6, 129.9, 130.0, 130.1, 131.1, 131.8, 139.9, 140.3, 145.3, 145.7, 166.5, 167.1; IR (neat,  $\text{cm}^{-1}$ ) 3027, 2983, 1723; HRMS calcd for  $\text{C}_{23}\text{H}_{20}\text{O}_4$ : 360.1362. Found: 360.1371. Anal. calcd for  $\text{C}_{23}\text{H}_{20}\text{O}_4$ : C, 76.65; H, 5.59. Found: C, 76.72; H, 5.47.

**Methyl 4-[2-(benzofuran-3-yl)phenyl]benzoate (4f).** This compound was prepared employing **5d** and **2a** under non-migration conditions for 6 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 75% yield of the indicated compound as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.87 (s, 3H), 7.11-7.14 (m, 1H), 7.21-7.27 (m, 2H), 7.30-7.34 (m, 3H), 7.42-7.49 (m, 4H), 7.58-7.60 (m, 1H), 7.87-7.89 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  52.3, 111.7, 120.6, 121.2, 123.0, 124.6, 127.4, 128.3, 128.4, 128.8, 129.5, 129.6, 130.1, 130.8, 131.1, 140.7, 143.1, 146.4, 155.3, 167.2; IR (neat,  $\text{cm}^{-1}$ ) 2973, 2850, 1723; HRMS calcd for  $\text{C}_{22}\text{H}_{16}\text{O}_3$ : 328.1099. Found: 328.1104.

**Methyl 4-[2-(1-methylindol-3-yl)phenyl]benzoate (4g).** This compound was prepared employing **5e** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 79% yield of the indicated compound as a white solid: mp 147-148  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.64 (s, 3H), 3.88 (s, 3H), 7.06 (t,  $J = 7.2$  Hz, 1H), 7.21 (t,  $J = 7.2$  Hz, 1H), 7.28 (d,  $J = 8.0$  Hz, 1H), 7.31 (d,  $J = 8.0$  Hz, 2H), 7.40 (m, 1H), 7.44 (m, 2H), 7.54 (d,  $J = 8.0$  Hz, 1H), 7.65 (d,  $J = 8.0$  Hz, 1H), 7.85 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.8, 52.1, 109.3, 114.9, 119.6, 119.9, 121.8, 126.6, 127.2, 128.0, 128.6, 129.2, 129.6, 130.6, 131.3, 133.5, 136.8, 140.0, 147.4, 167.2; IR (neat,  $\text{cm}^{-1}$ ) 3056, 2950, 1719; HRMS calcd for  $\text{C}_{23}\text{H}_{19}\text{NO}_2$ : 341.1416. Found: 341.1422. Anal. calcd for  $\text{C}_{23}\text{H}_{19}\text{NO}_2$ : C, 80.92; H, 5.61; N, 4.10. Found: C, 80.67; H, 5.44; N, 3.99.

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**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all new compounds. This material is included in Appendix D and is also available free of charge via the Internet at <http://interscience.wiley.com>.

## References

1. (a) Tsuji, J. In *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, John Wiley & Sons, New York, 1995. (b) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, New York, 2002.
2. For palladium migration along a carbon chain, see: (a) Larock, R. C.; Wang, Y. *Tetrahedron Lett.* **2002**, *43*, 21. (b) Larock, R. C.; Wang, Y.; Lu, Y.-D.; Russell, C. E. *J. Org. Chem.* **1994**, *59*, 8107. (c) Larock, R. C.; Lu, Y.-D.; Bain, A. C.; Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589, and references therein. For palladium migration through space, see: (d) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372. (e) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (f) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (g) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725. (h) Heck, R. F. *J. Organomet. Chem.* **1972**, *37*, 389.
3. For recent reviews on Suzuki coupling, see: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
4. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
5. (a) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466. (b) Netherton, M. R.; Dai, C.; Neushutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
6. Campo, M. A. Ph.D. Dissertation, Iowa State University, 2002.
7. Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.
8. Murray, M. M.; Kaszynski, P.; Kaisaki, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 8152.
9. Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447.

10. Ibuki, E.; Ozasa, S.; Fujioka, Y.; Yanogihara, Y. *Chem. Pharm. Bull.* **1982**, *30*, 802.
11. Trost, B. M.; Arndt, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 5288.
12. Hanson, G.; Kemp, D. S. *J. Org. Chem.* **1981**, *46*, 5441.
13. Freeman, P. K.; Tafesh, A. M.; Clapp, G. E. *J. Org. Chem.* **1989**, *54*, 782.

## GENERAL CONCLUSION

The isolation and synthesis of naturally occurring carbolines and the synthesis of  $\beta$ - and  $\gamma$ -carboline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance. In this dissertation, we have investigated new palladium approaches to the synthesis of a variety of  $\beta$ - and  $\gamma$ -carboline derivatives.

Chapter 1 describes the synthesis of a variety of 3,4-disubstituted  $\beta$ - and  $\gamma$ -carbolines by the palladium-catalyzed iminoannulation of internal alkynes. This chemistry tolerates various functional groups on the alkyne and can be extended to terminal alkynes to synthesize a variety of 3-substituted  $\beta$ - and  $\gamma$ -carbolines. Two biologically interesting  $\beta$ -carboline alkaloids, ZK93423 and abecarnil, have also been synthesized by employing this palladium-catalyzed iminoannulation methodology.

Chapter 2 describes in detail, the synthesis of 3-substituted  $\beta$ - and  $\gamma$ -carboline derivatives by the palladium/copper-catalyzed coupling and cyclization of terminal alkynes, which is complementary to our annulation chemistry described in Chapter 1. This chemistry also tolerates various functional groups on the terminal alkynes and affords good to excellent yields of the desired  $\beta$ - and  $\gamma$ -carbolines.

Chapter 3 presents an extension of our intermolecular iminoannulation chemistry described in Chapter 1 to intramolecular iminoannulation, by which a variety of annulated  $\gamma$ -carbolines with an additional ring fused across the 4- and 5-positions can be synthesized in good to excellent yields. This "intramolecular" concept has also been extended to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

Chapter 4 presents relatively independent chemistry involving a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids. Various *o*-iodobiaryls and arylboronic acids with different electronic properties have been examined. It has been found that palladium prefers to migrate from a more electron-deficient position to a more electron-rich position in the biaryl.

## **ACKNOWLEDGMENTS**

First of all, I would like to express my sincere gratitude to my major professor, Dr. Richard C. Larock for his encouragement, trust, and academic and financial support throughout my graduate studies at Iowa State University. I have to agree that he is truly the best research advisor that a graduate student can work with.

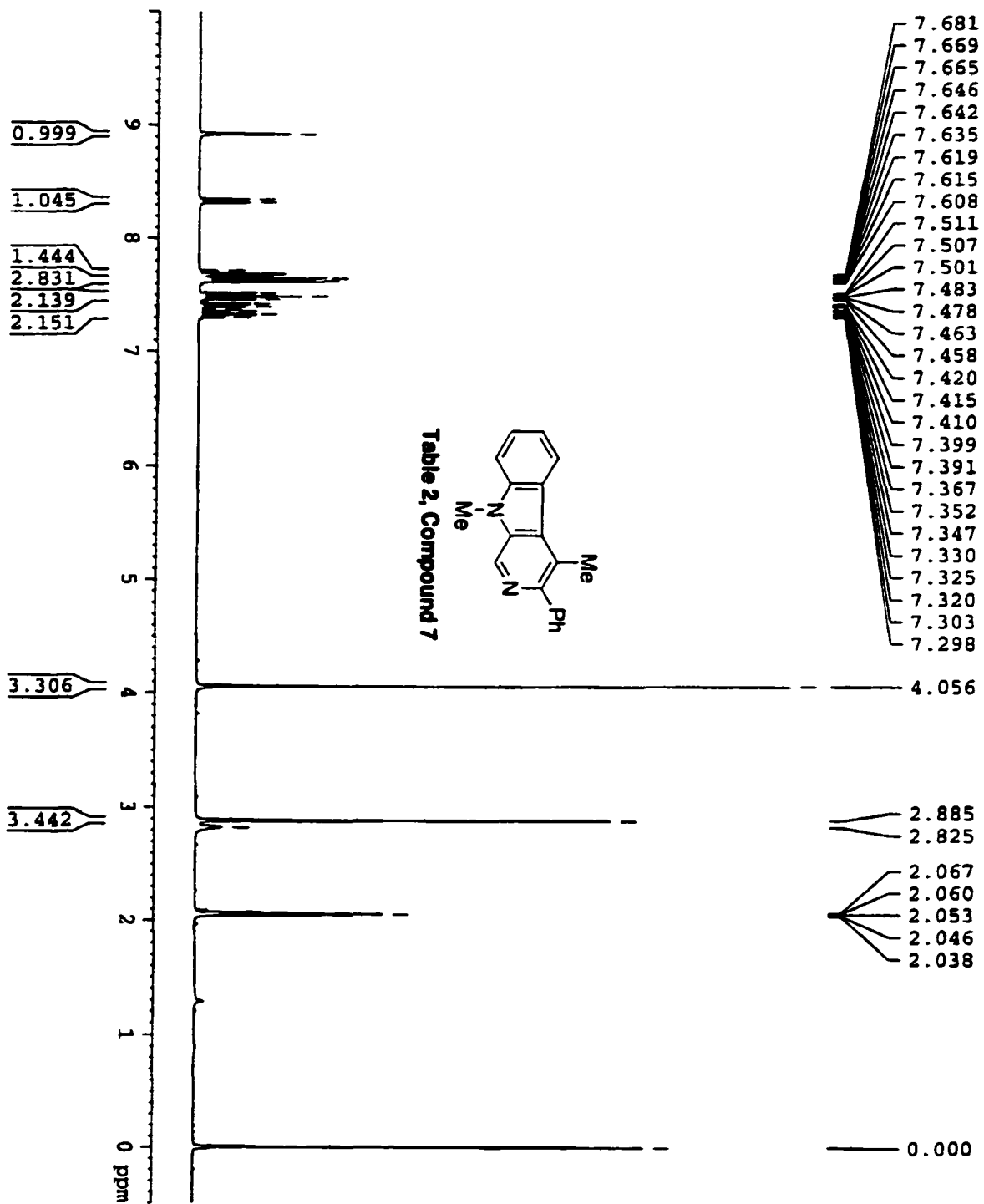
I have met so many great professors and students in the past five years at Iowa State University who have helped me through a number of things. I have to thank all the professors who have taught me fascinating chemistry; I also want to thank all my committee members for providing me both academic and personal help. I want to thank the past members of the Larock group that I have worked with: Dr. Kevin Roesch, Dr. Steve Gagnier, Dr. Dan Emrich, Dr. Alex Pletnev, Dr. Dmitry Kadnikov, Jack Hunter, Li Zhang, Hao Yin, Daohua Zhang, and especially Dr. Marino Campo, with whom I worked in the same lab for four years and from whom I received numerous exciting ideas. I can't allow myself to forget to thank the current members of the Larock group: Dr. Fengkui Li, Guangxiu Dai, Roman Rhozkov, Qinhua Huang, Dawei Yue, Xiaoxia Zhang, Tuanli Yao, Chengxiang Zhou, Zhijian Liu and Jian Zhao. Some of you guys really helped me a lot in the laboratory. Anyways, it has been my great pleasure being with all of you guys.

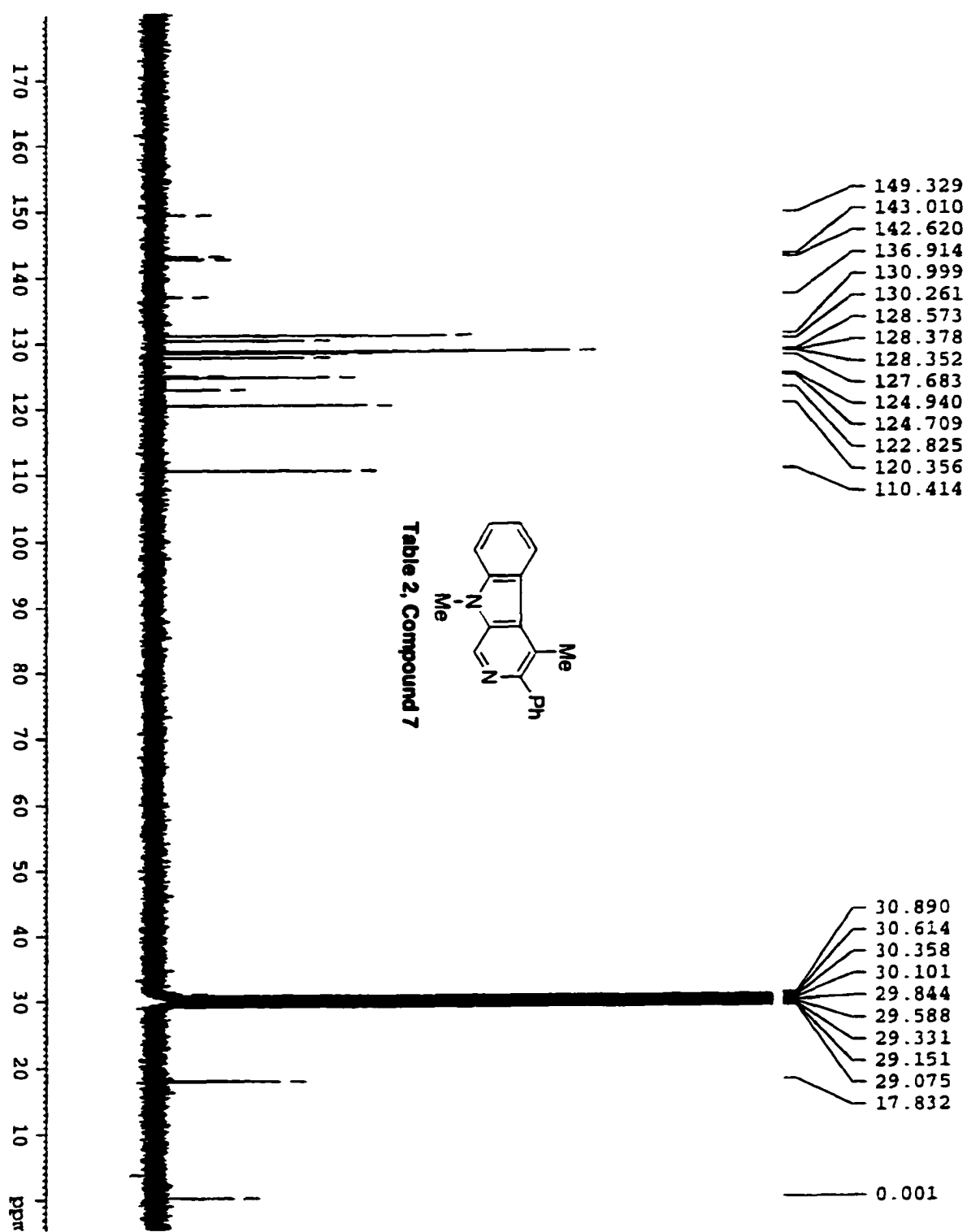
I would like to thank my parents and my parents-in-law, even though I am sure they cannot understand what I have been working on. It's been five long years that my wife and I haven't called you "dad and mom" face to face!

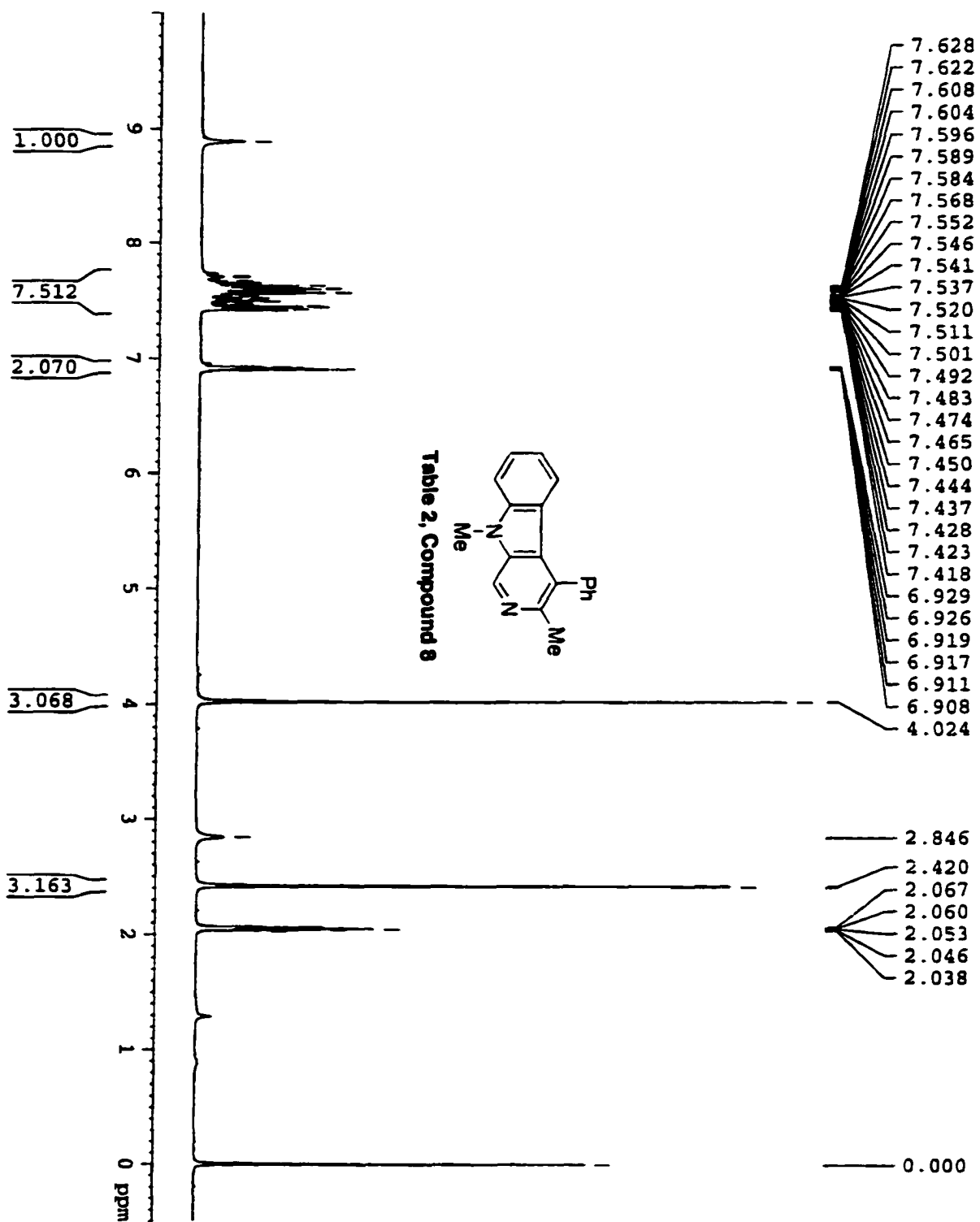
Finally, I want to thank my lovely wife, Ye Gu, for her loving support, patience, understanding, and incredible sacrifices during my five years here at Iowa State. We still need to get through the coming two years of my postdoctoral career in Pasadena.

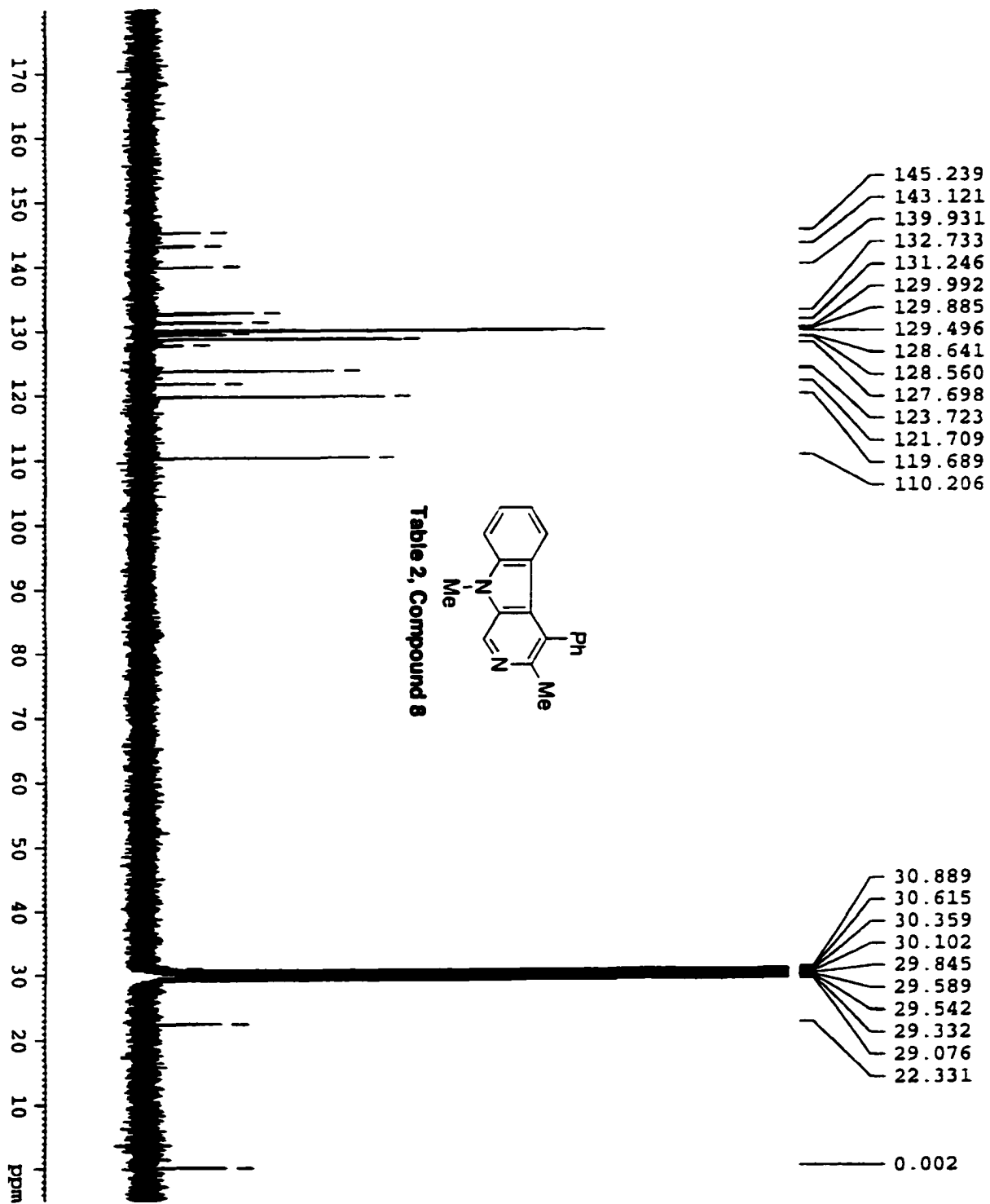


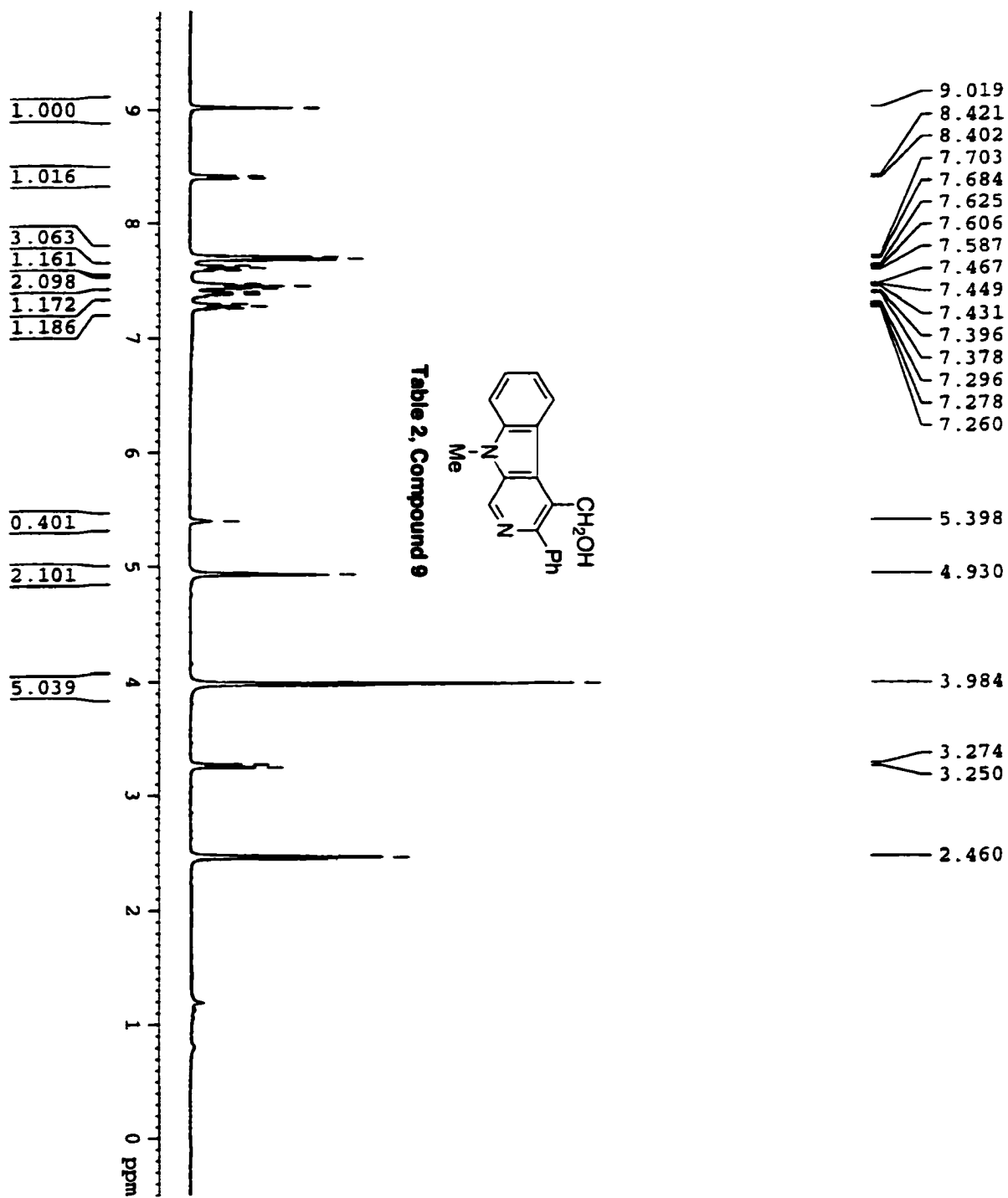
**APPENDIX A. CHAPTER 1  $^1\text{H}$  AND  $^{13}\text{C}$  NMR SPECTRA**

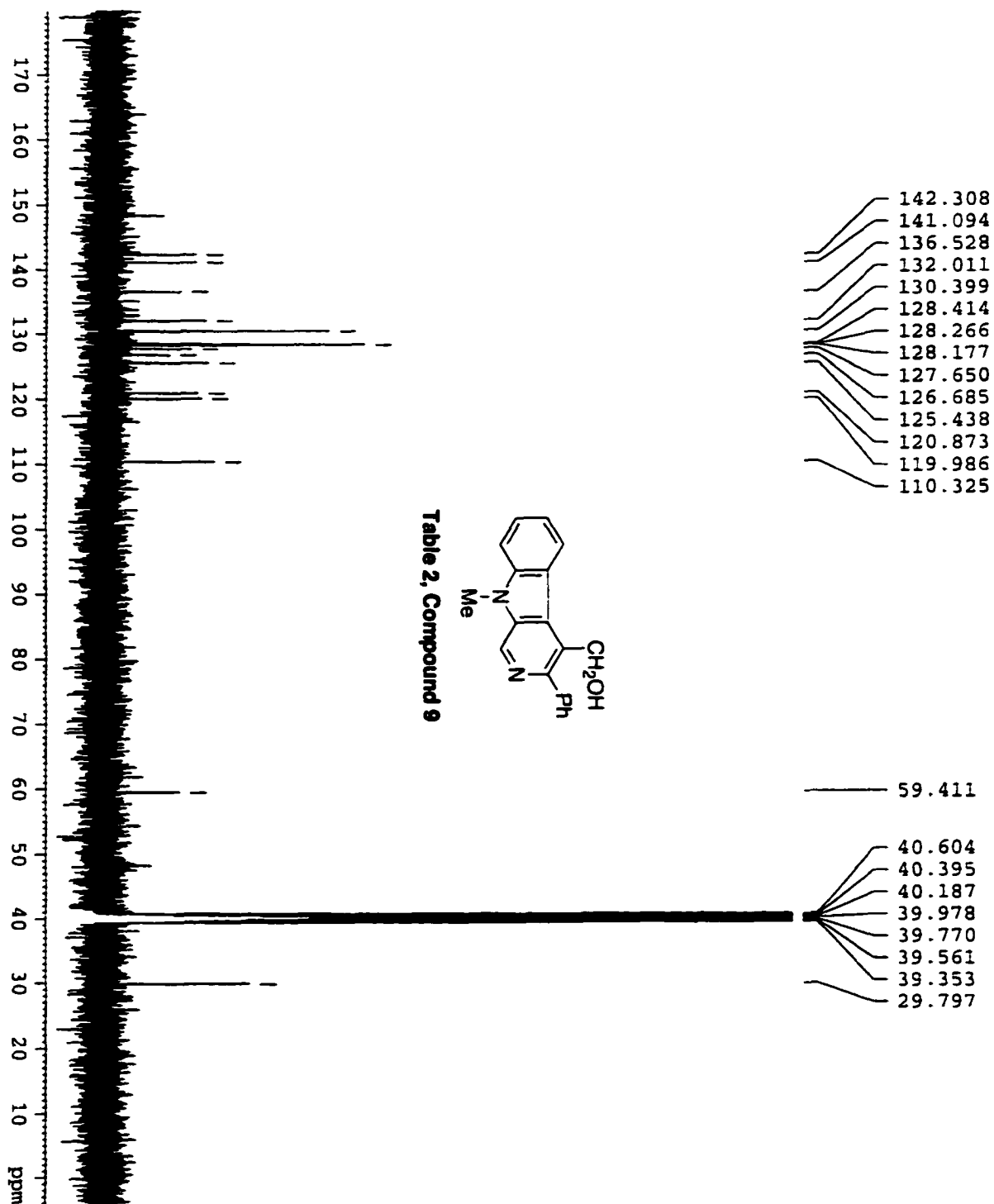


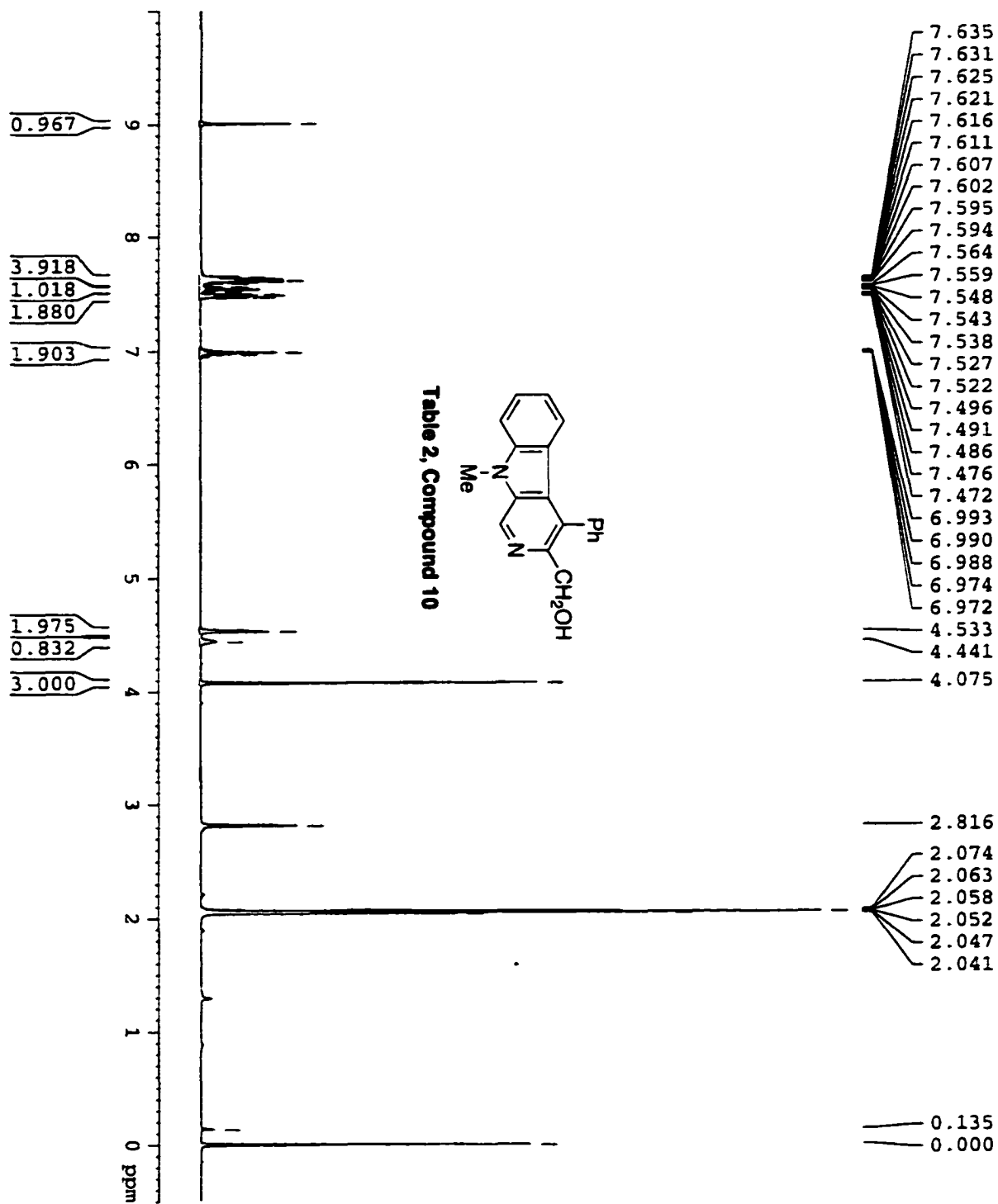




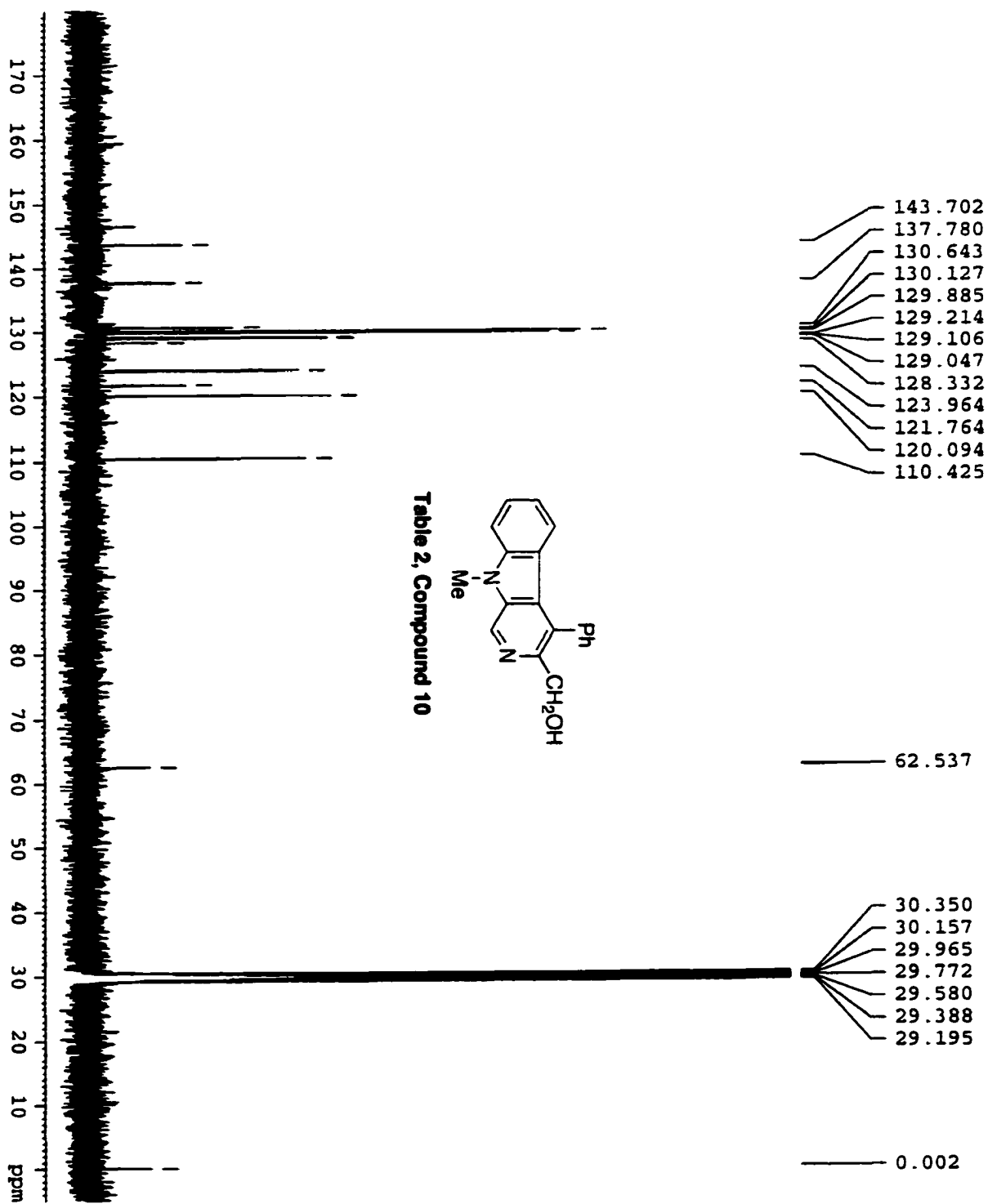


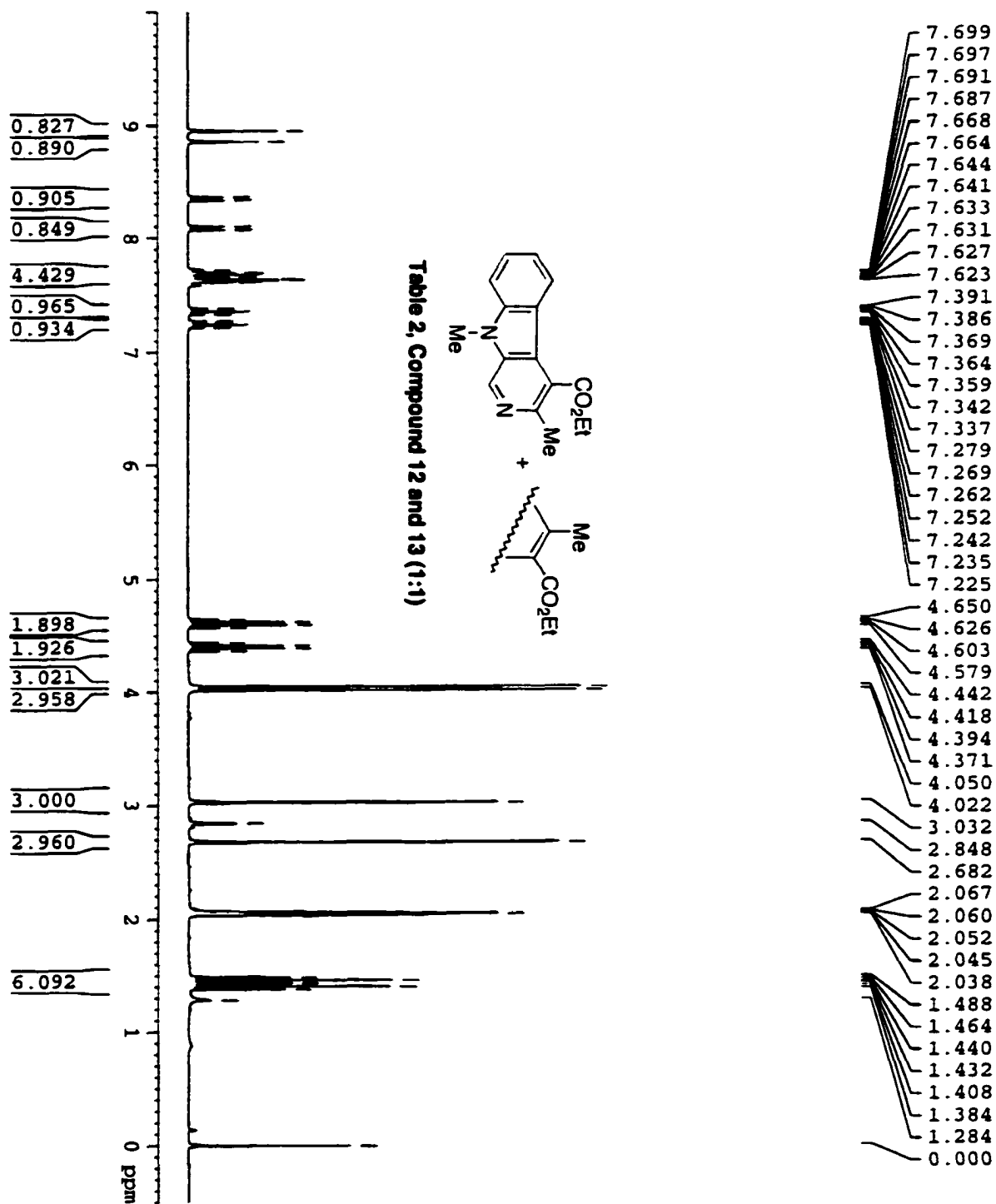


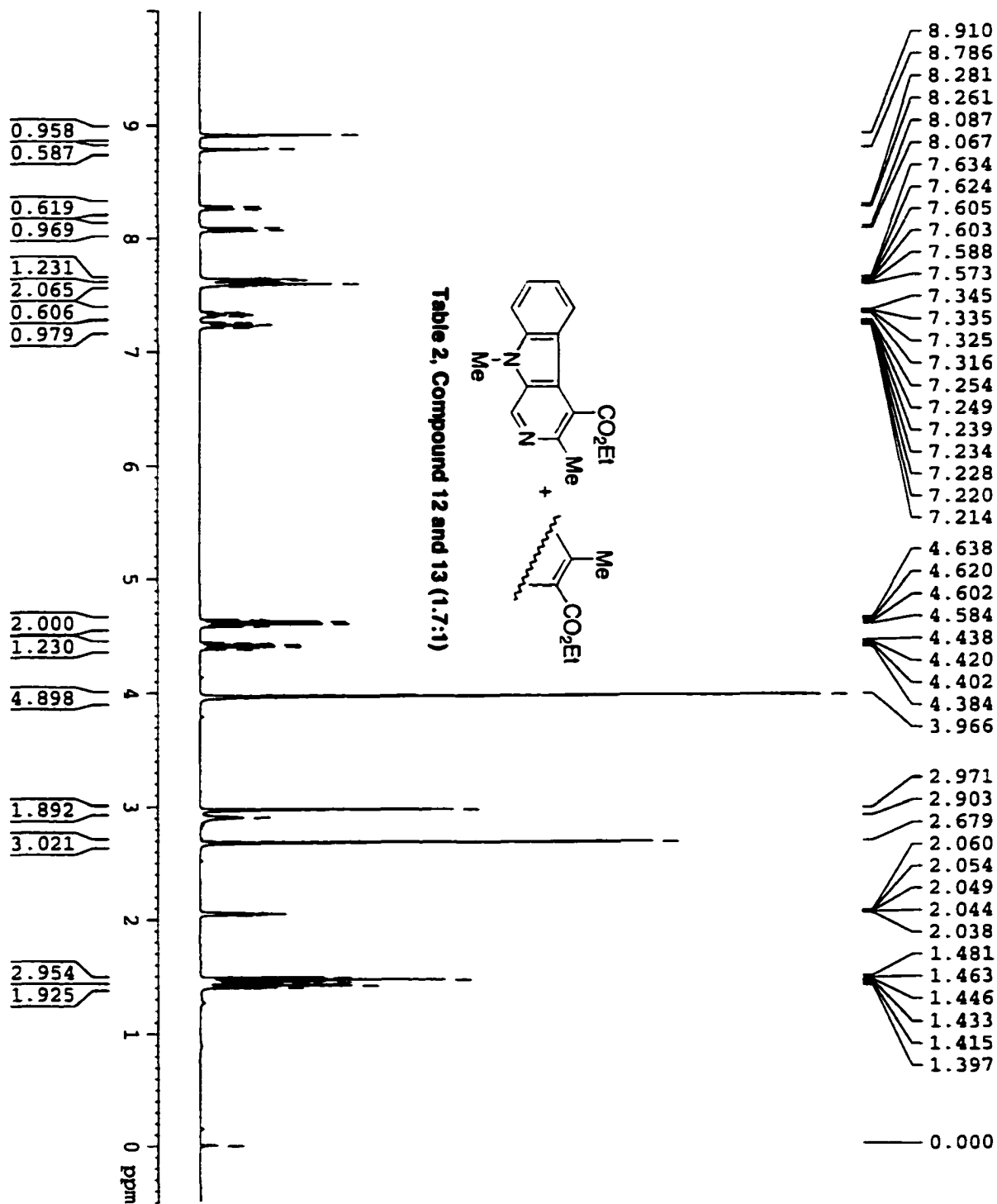


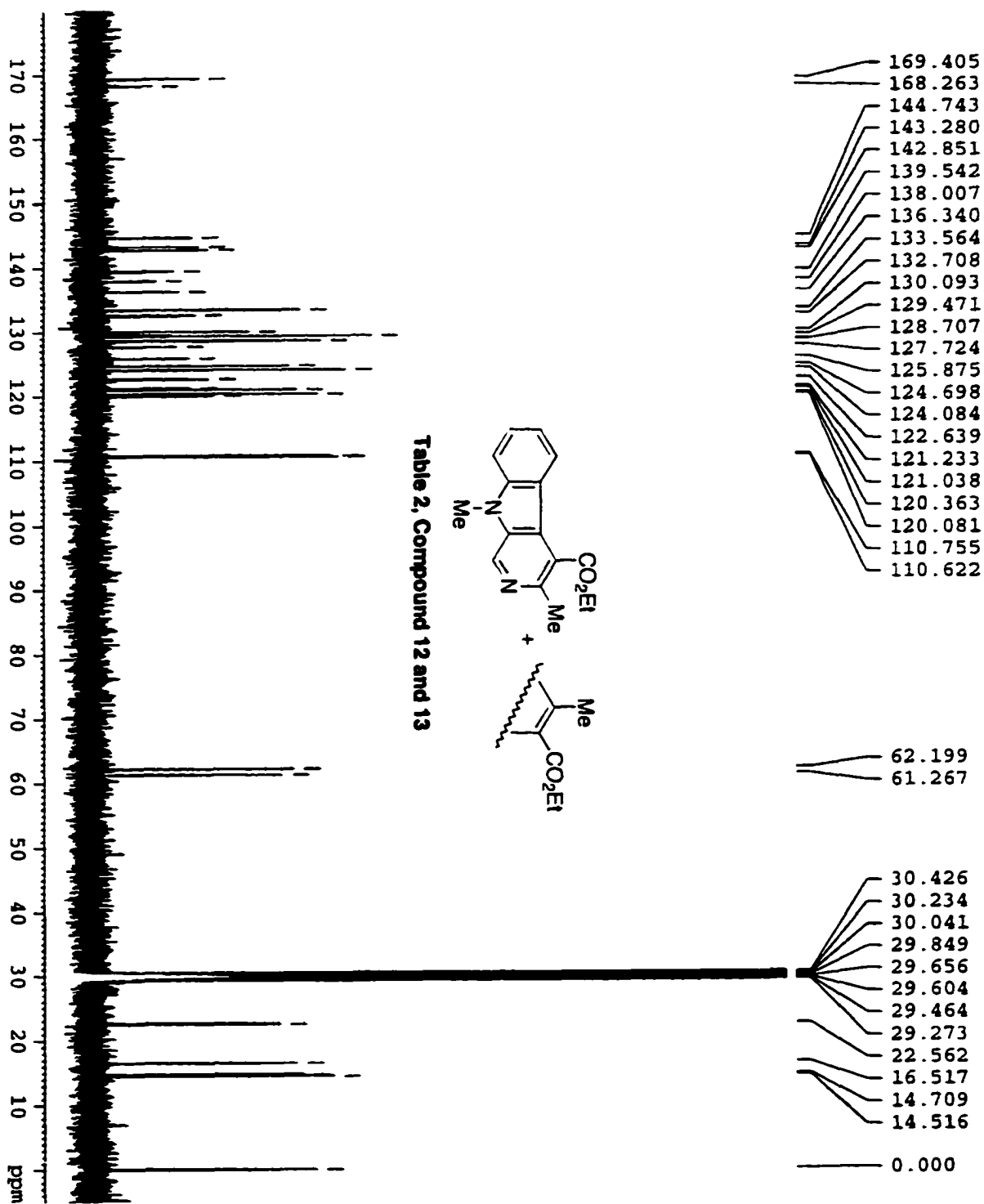


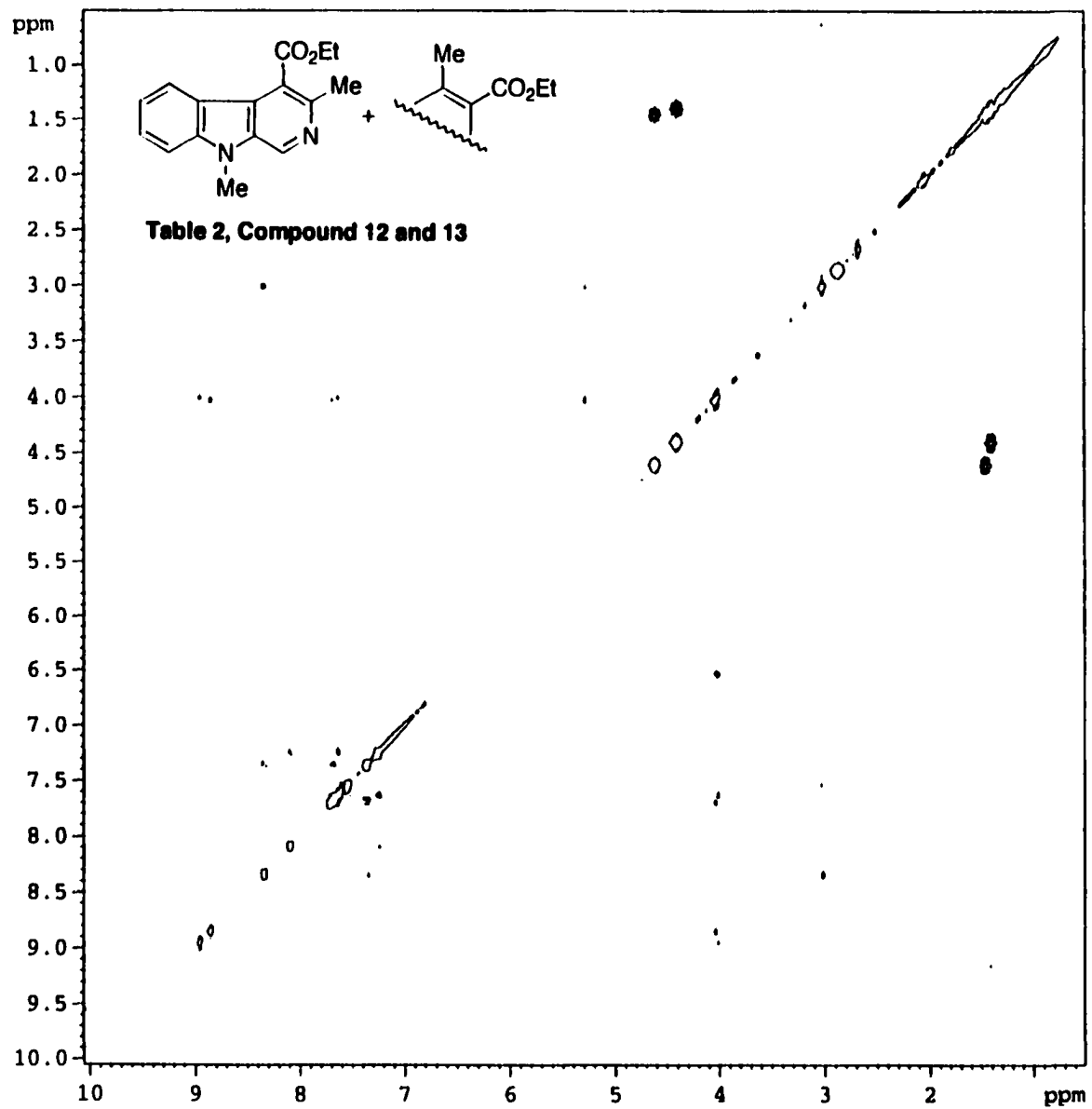


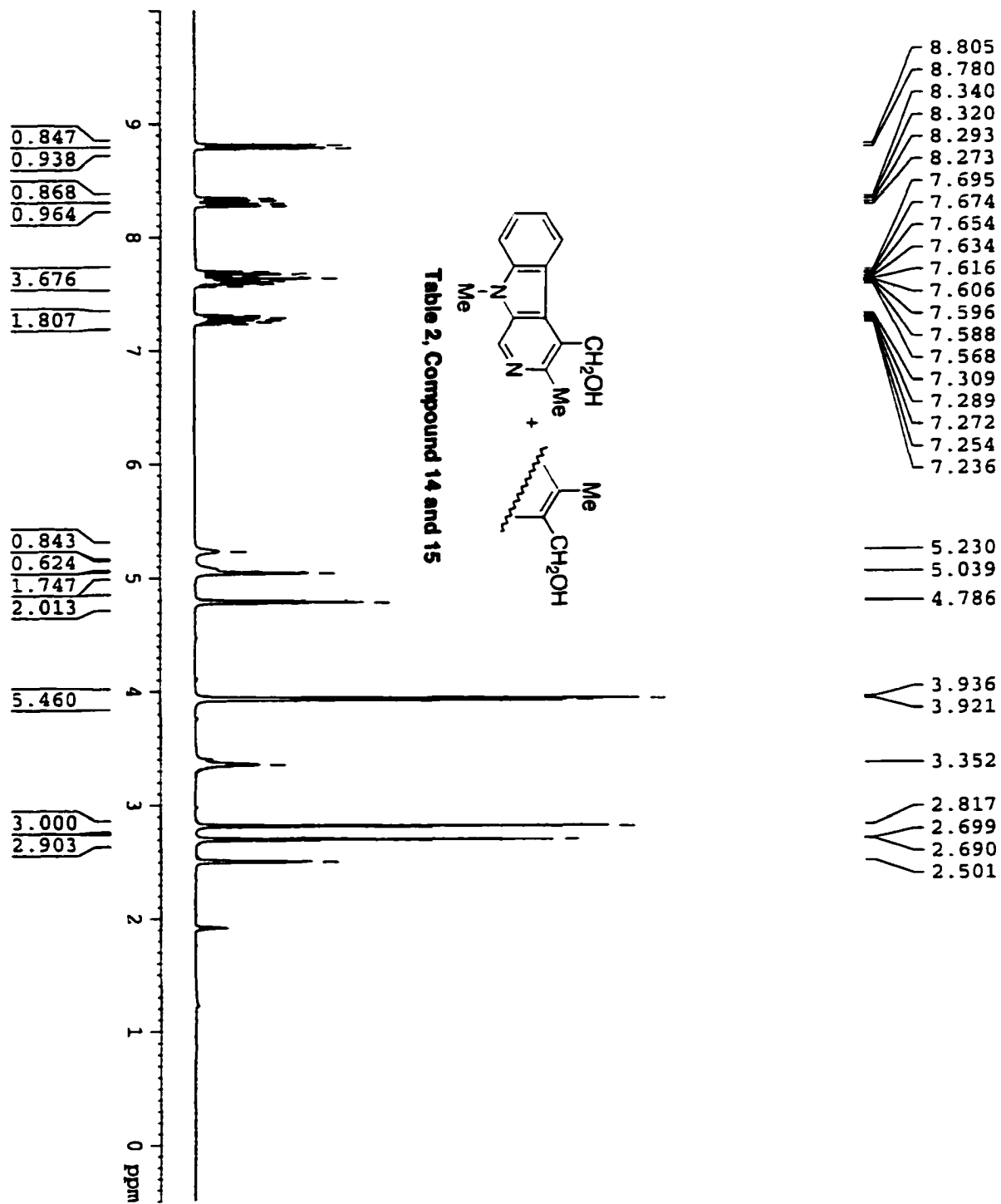


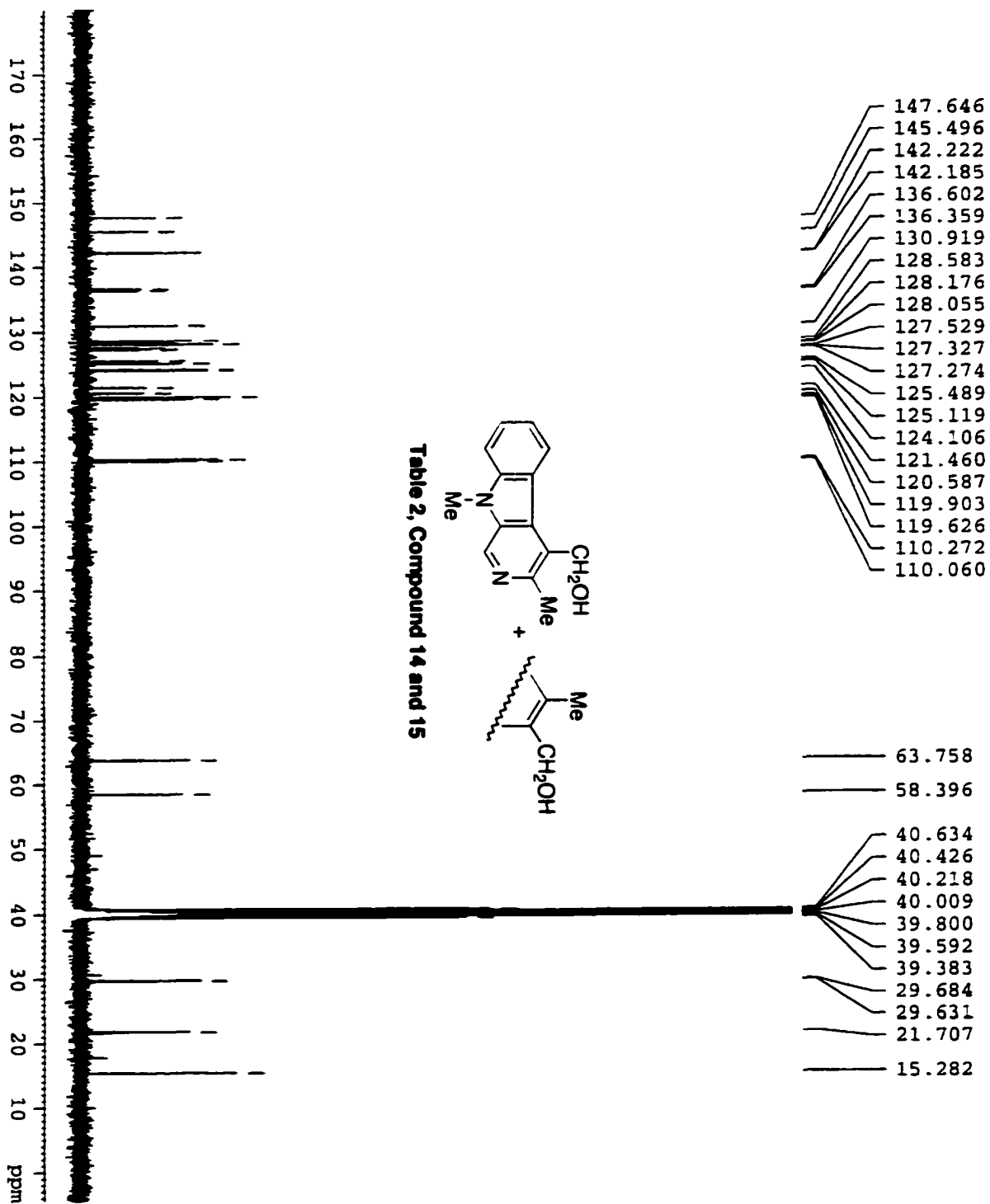


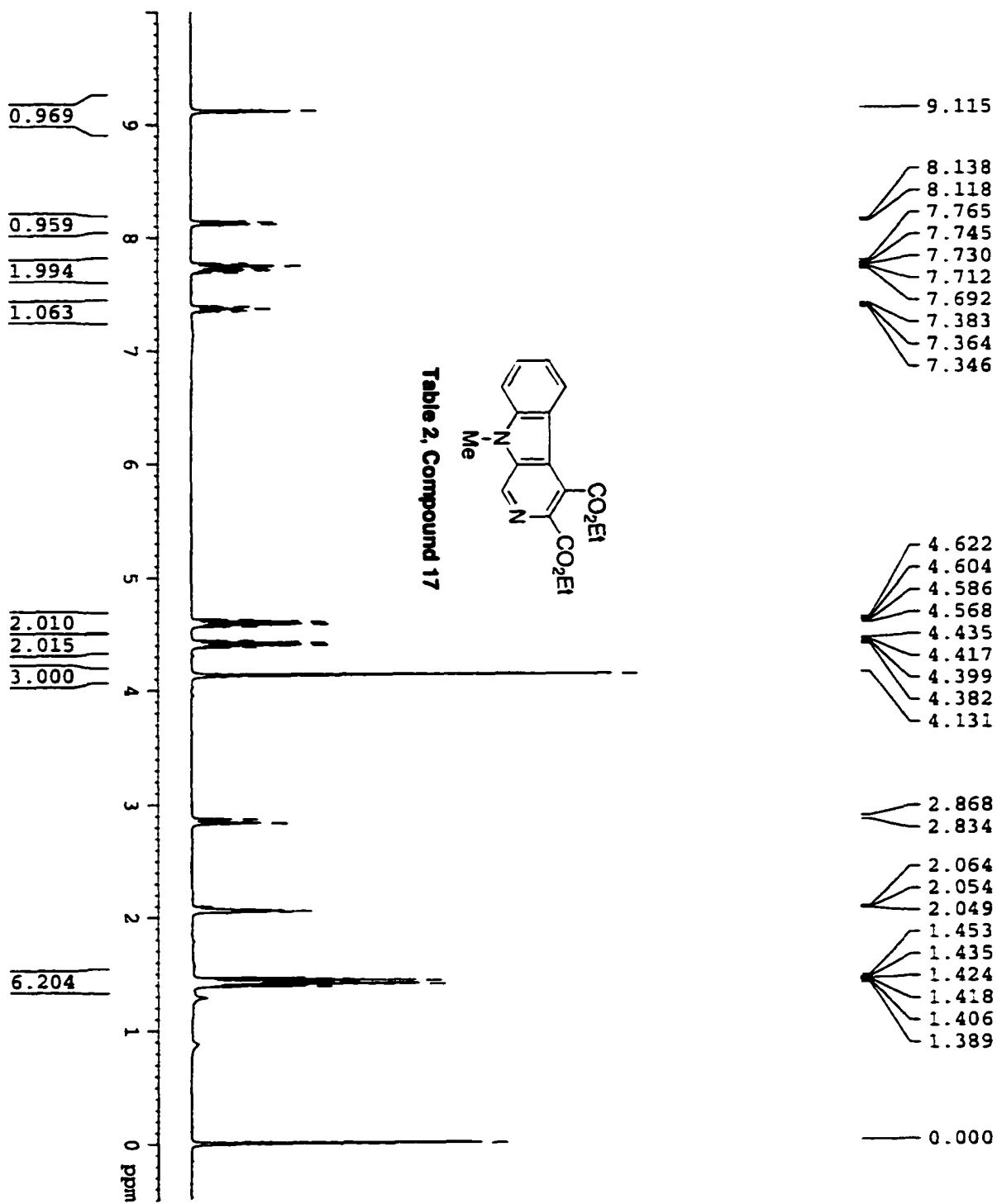




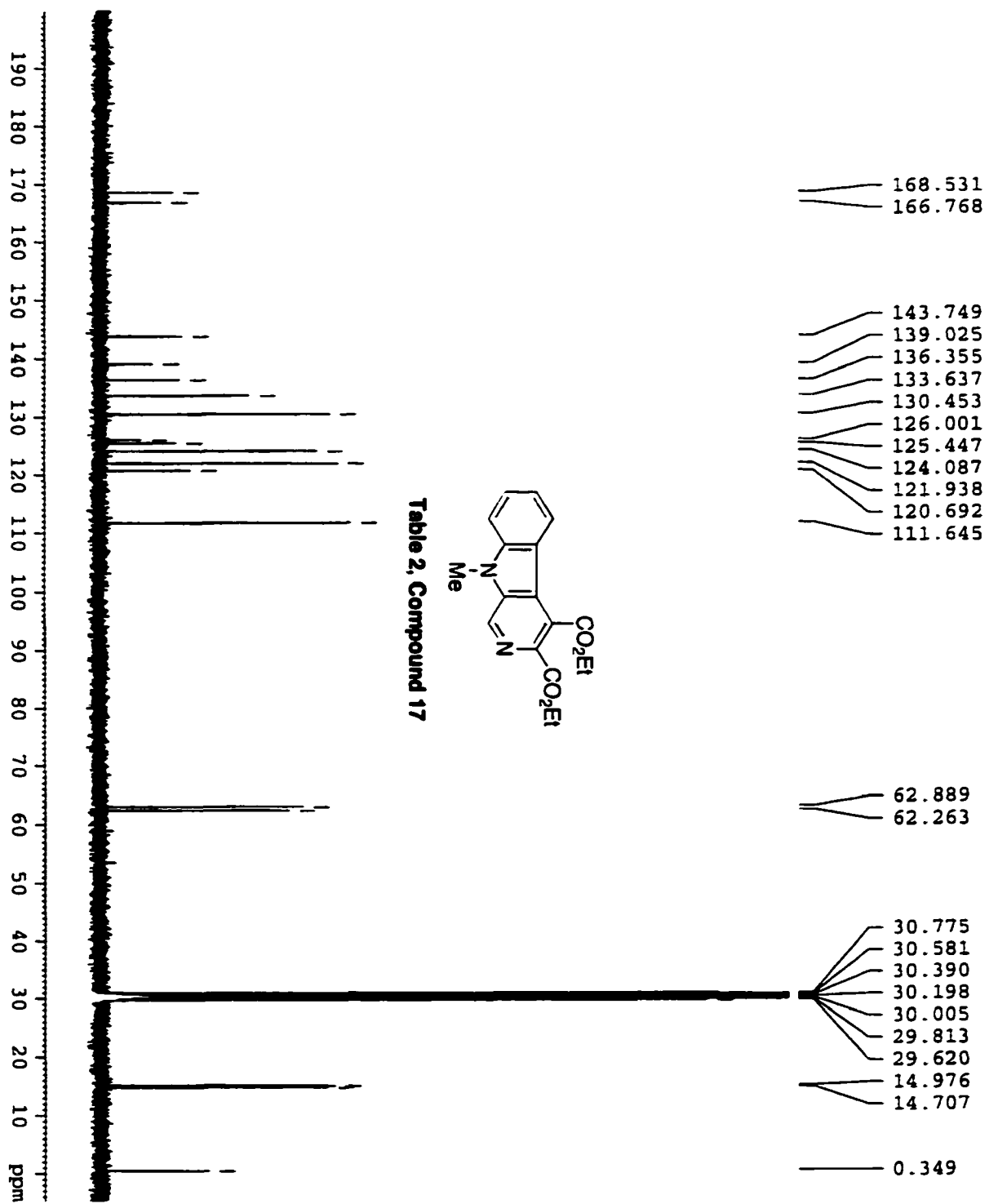


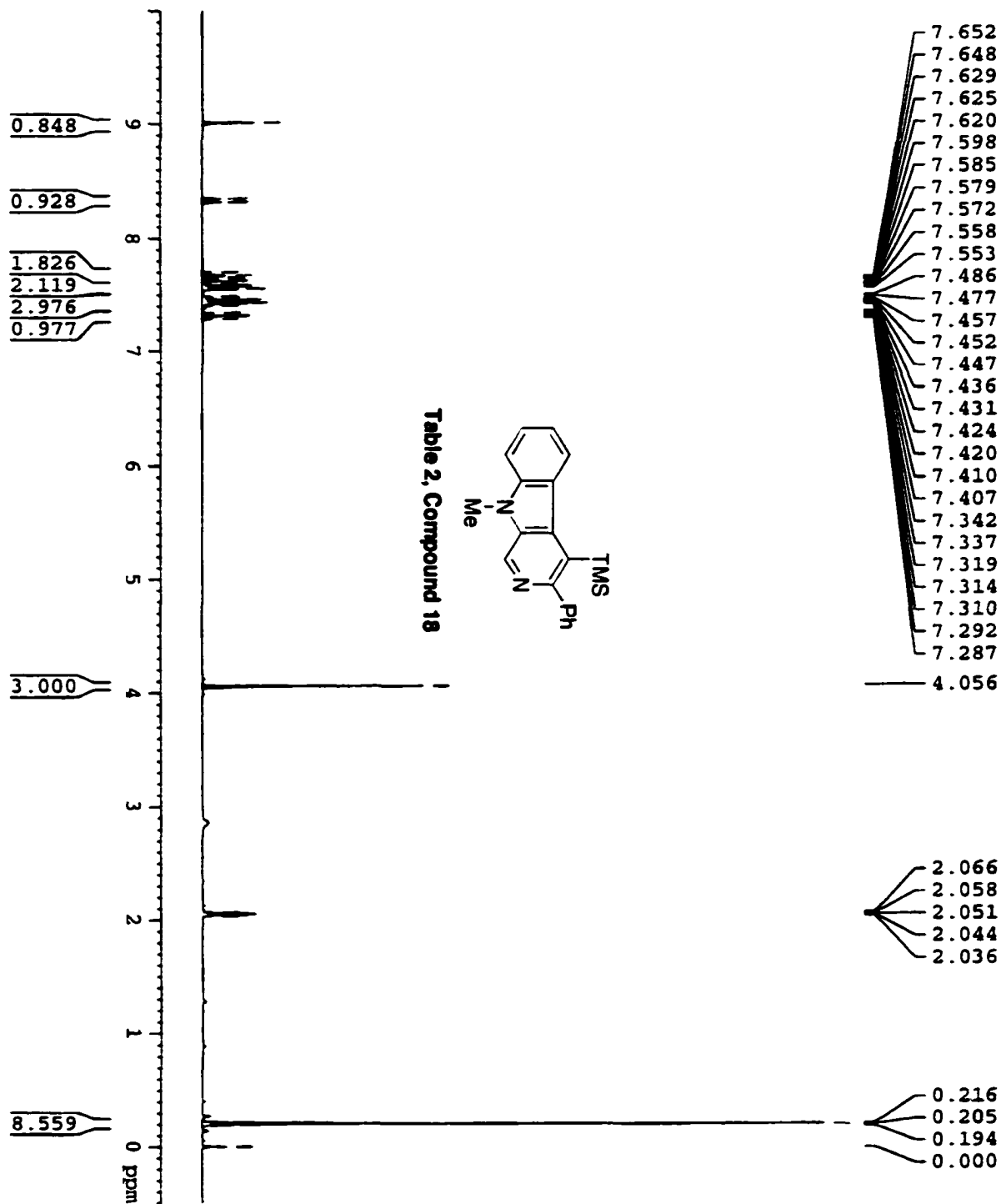


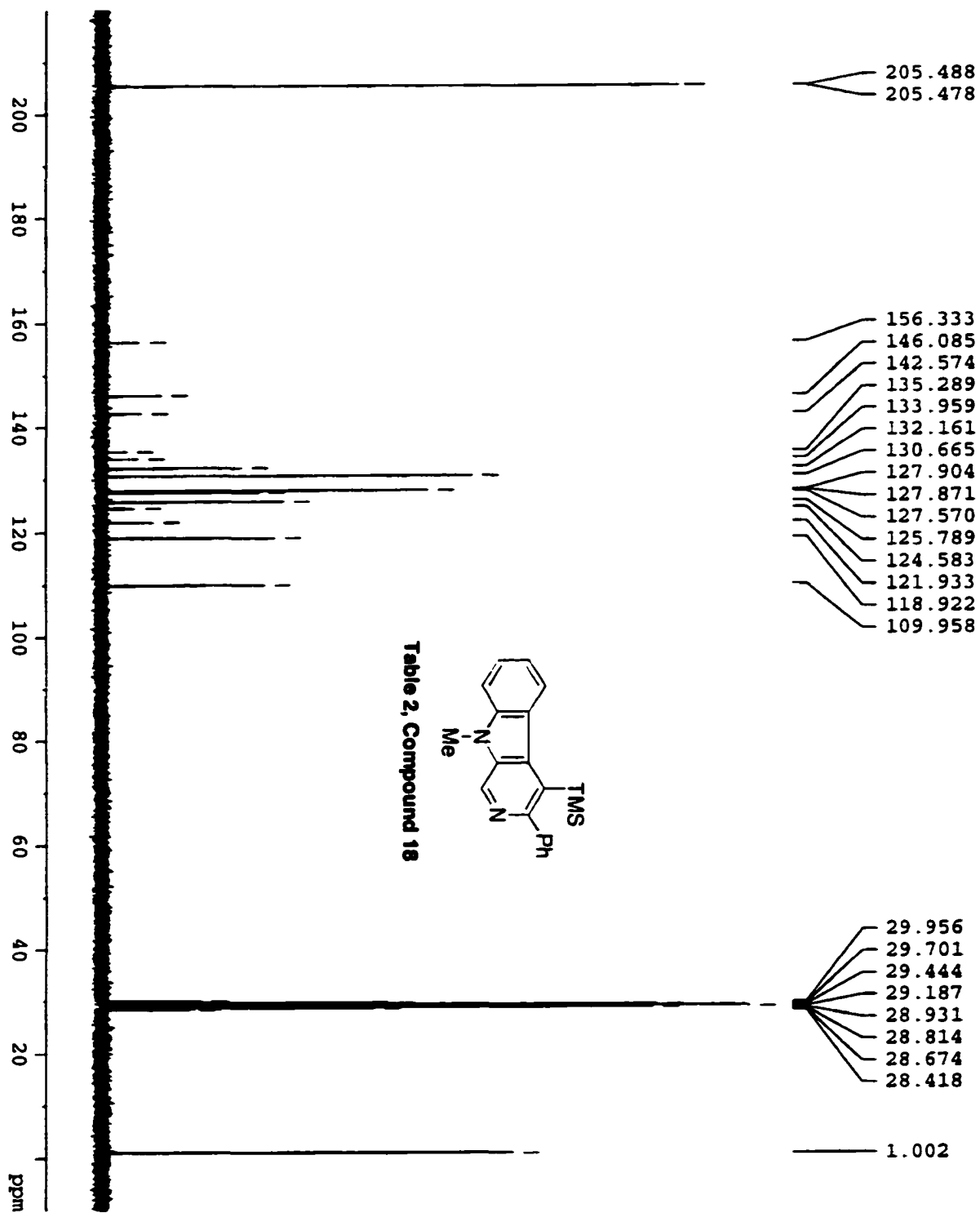












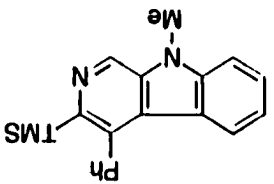
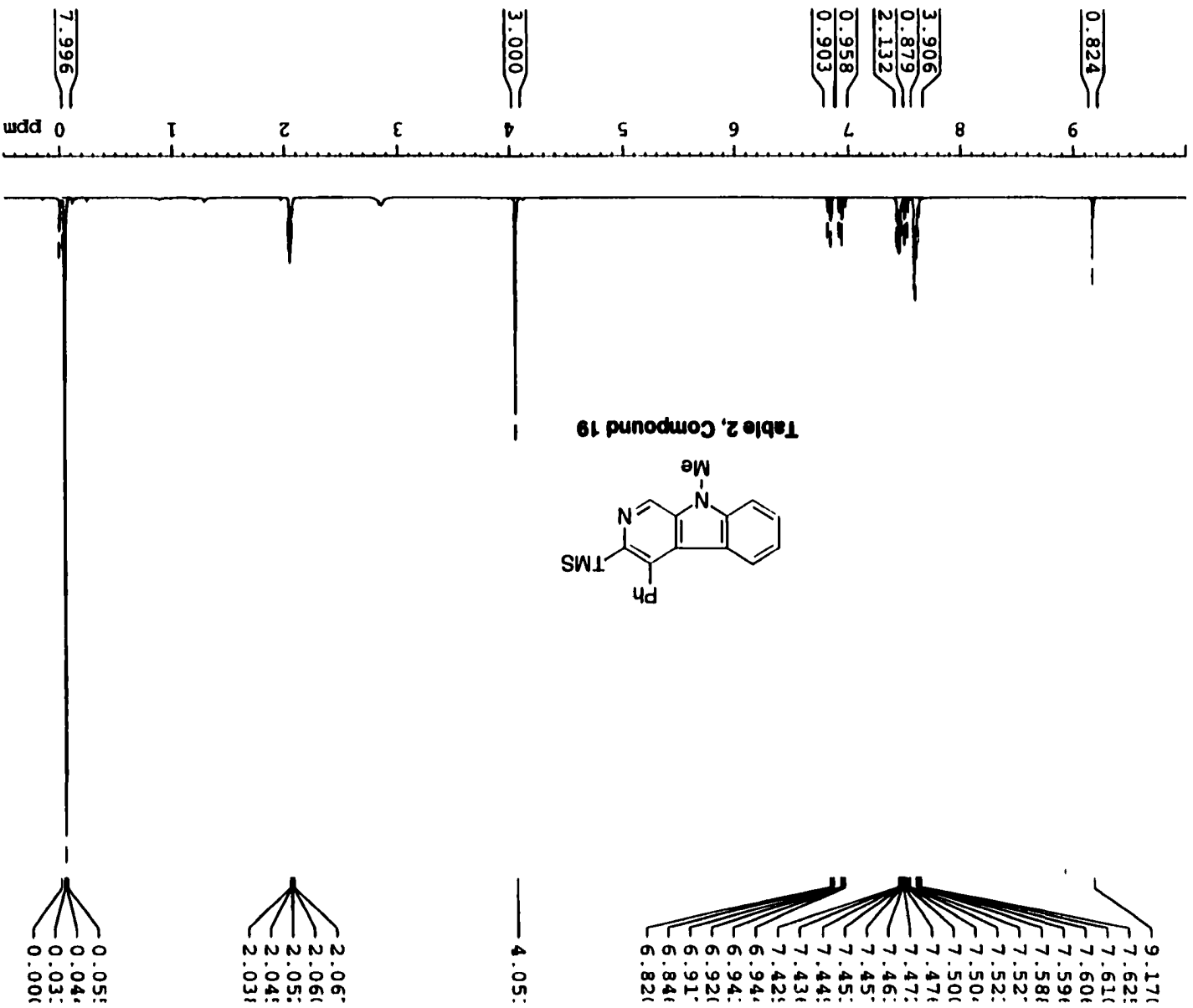
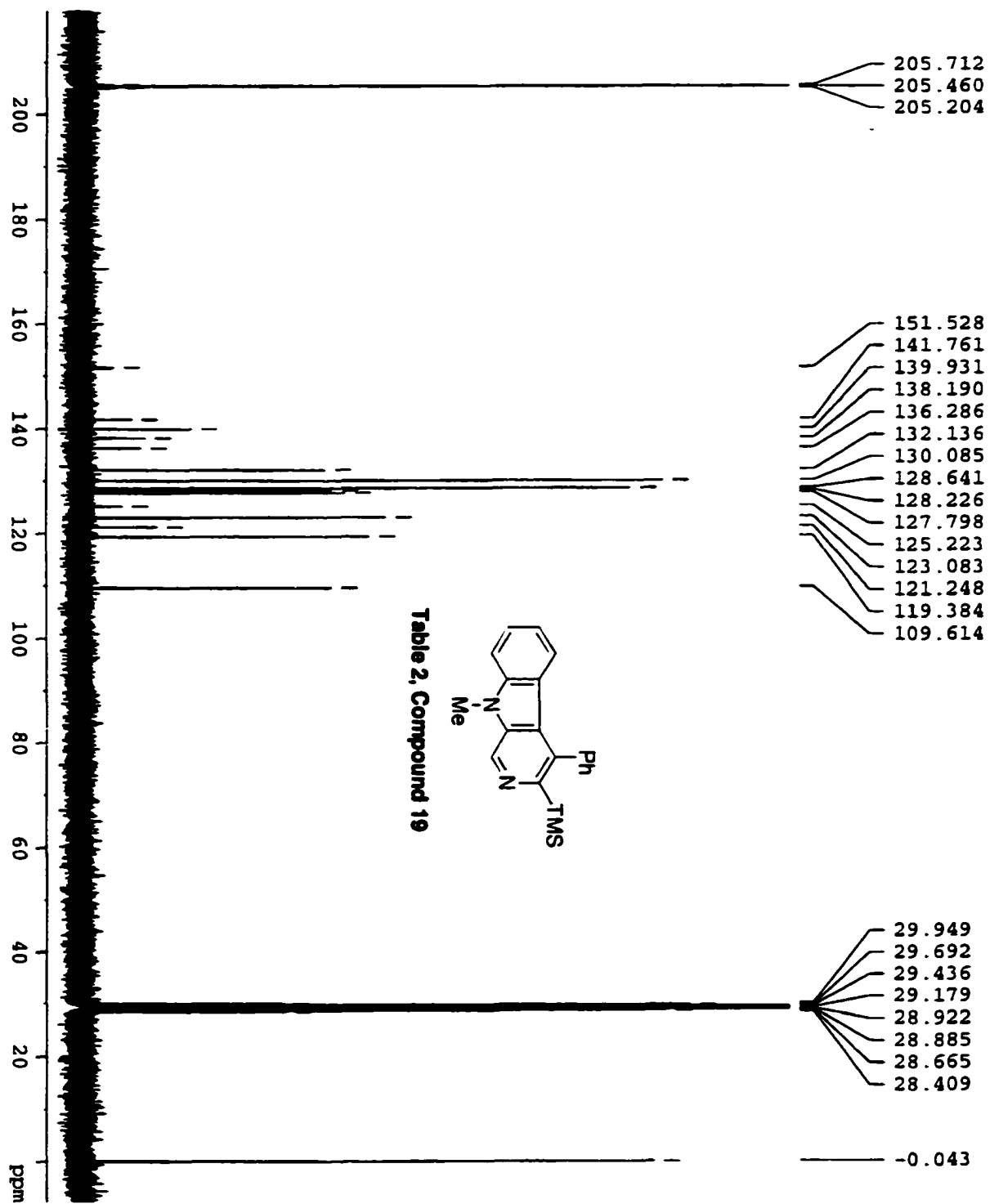
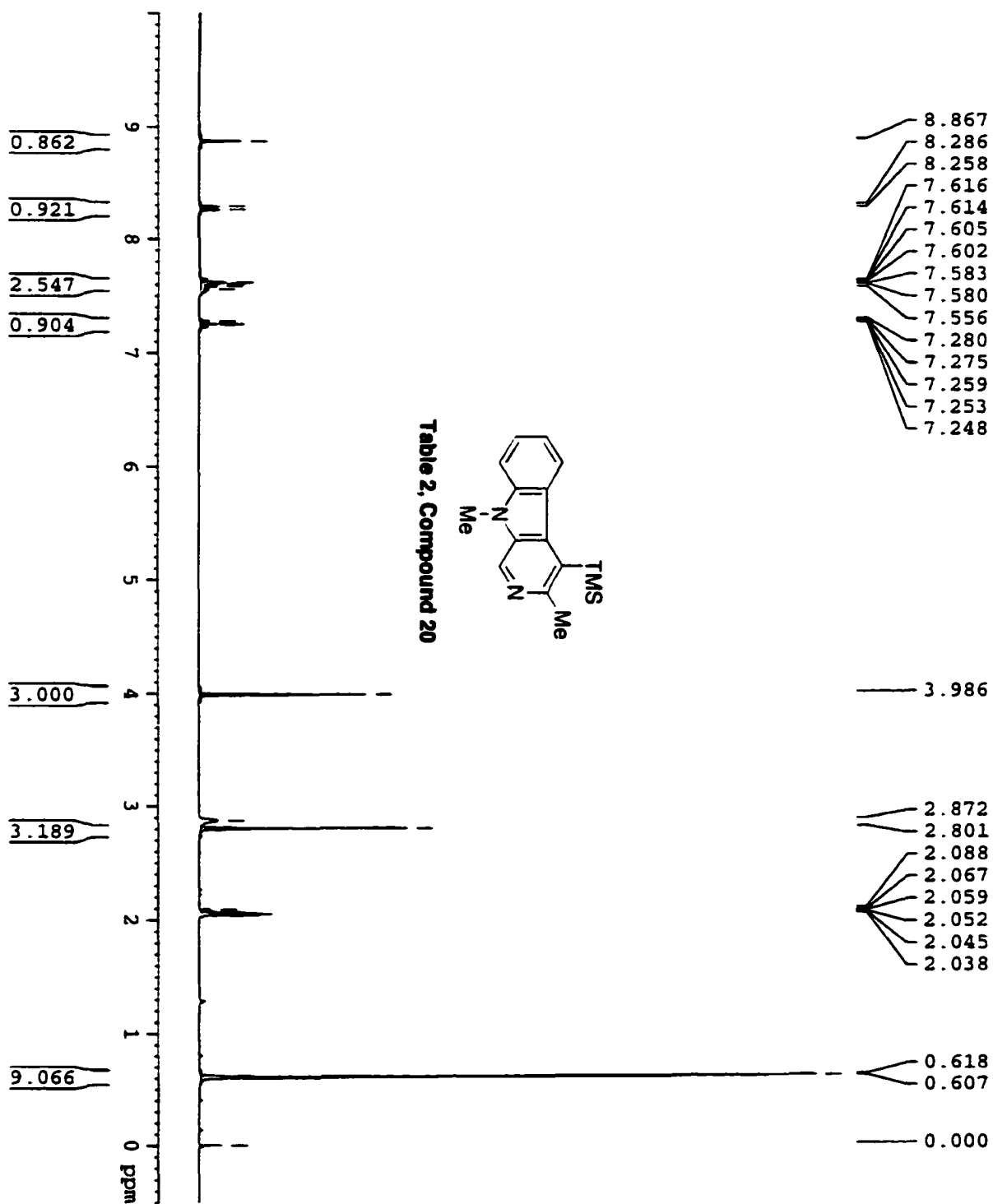
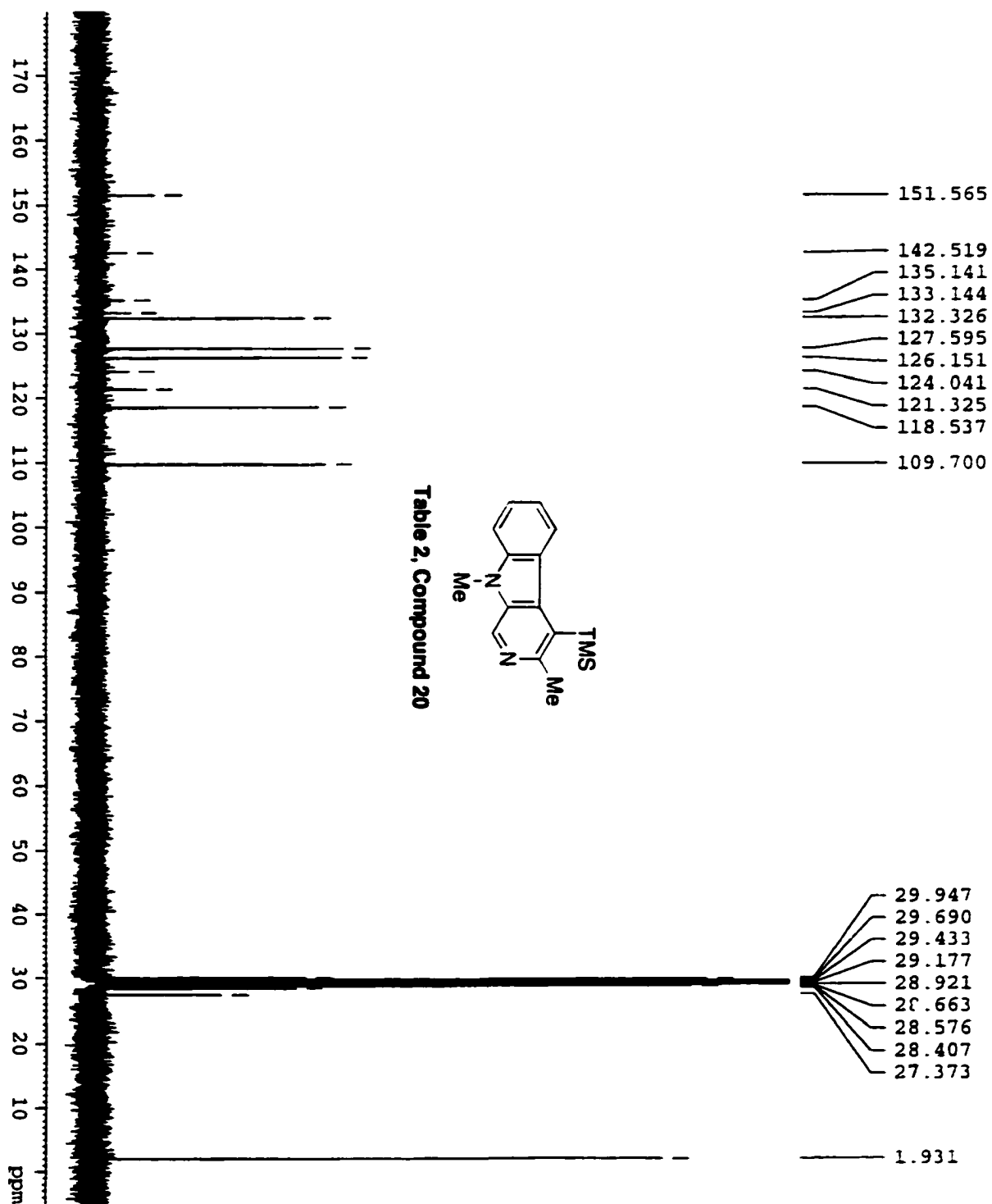


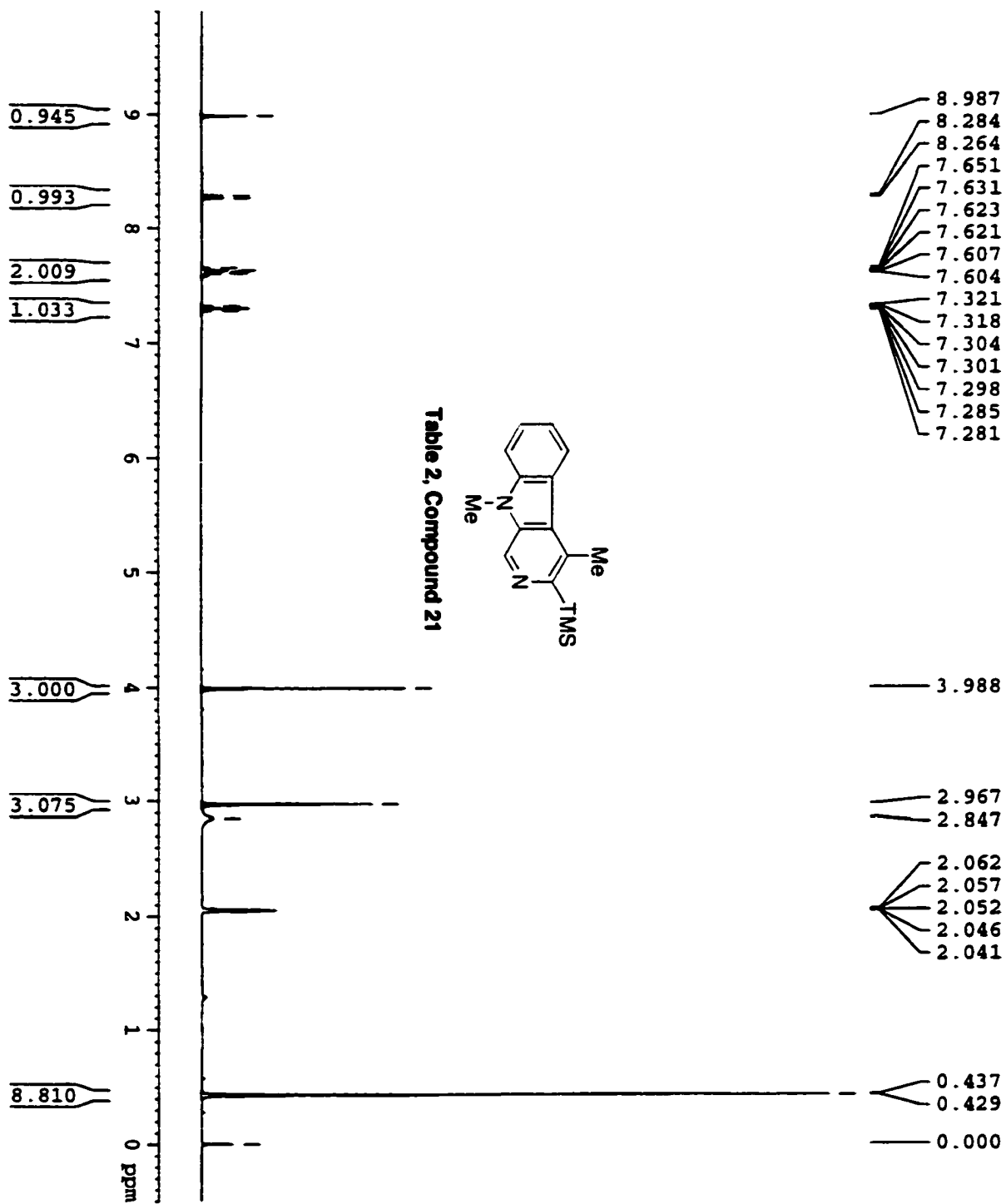
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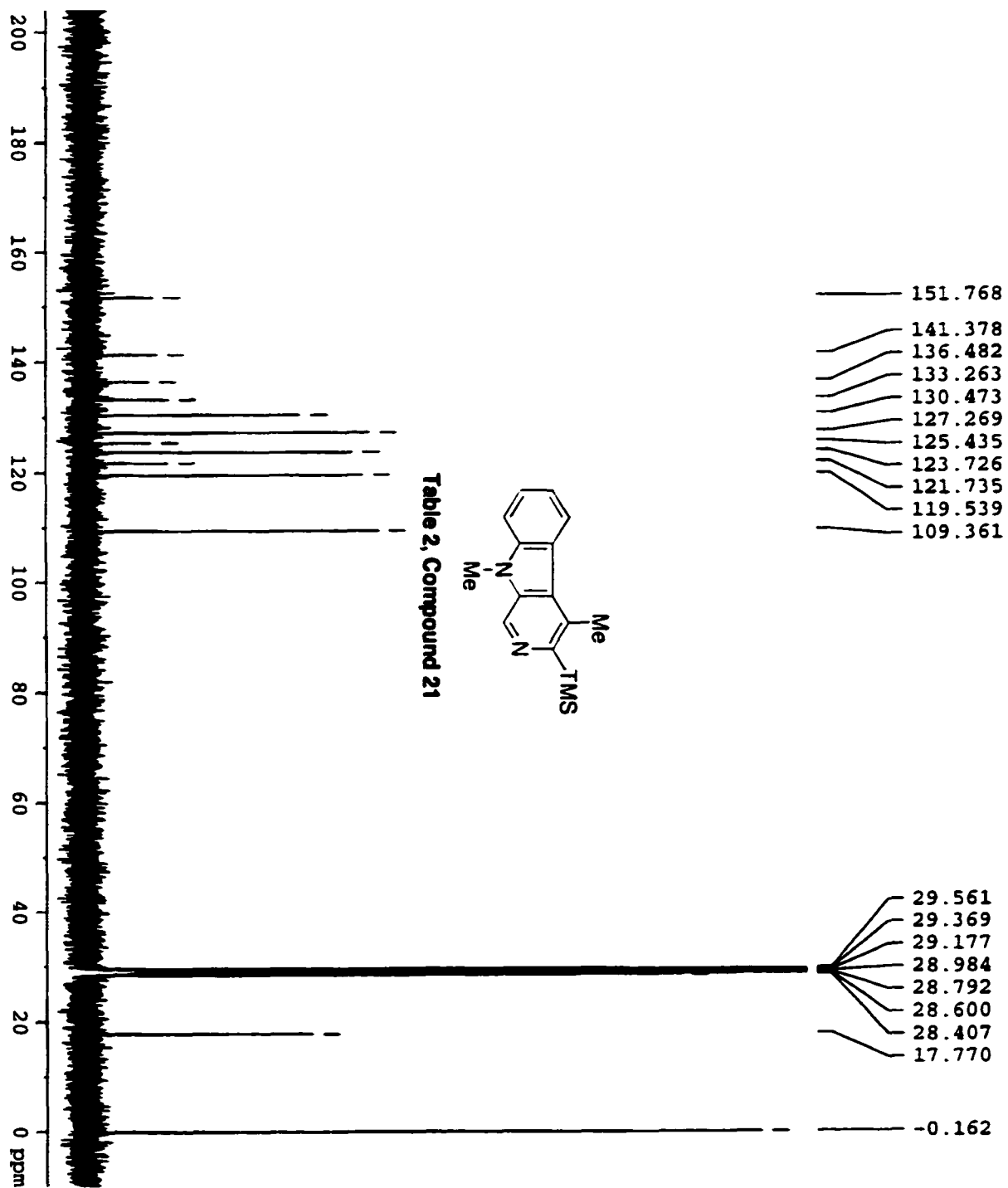


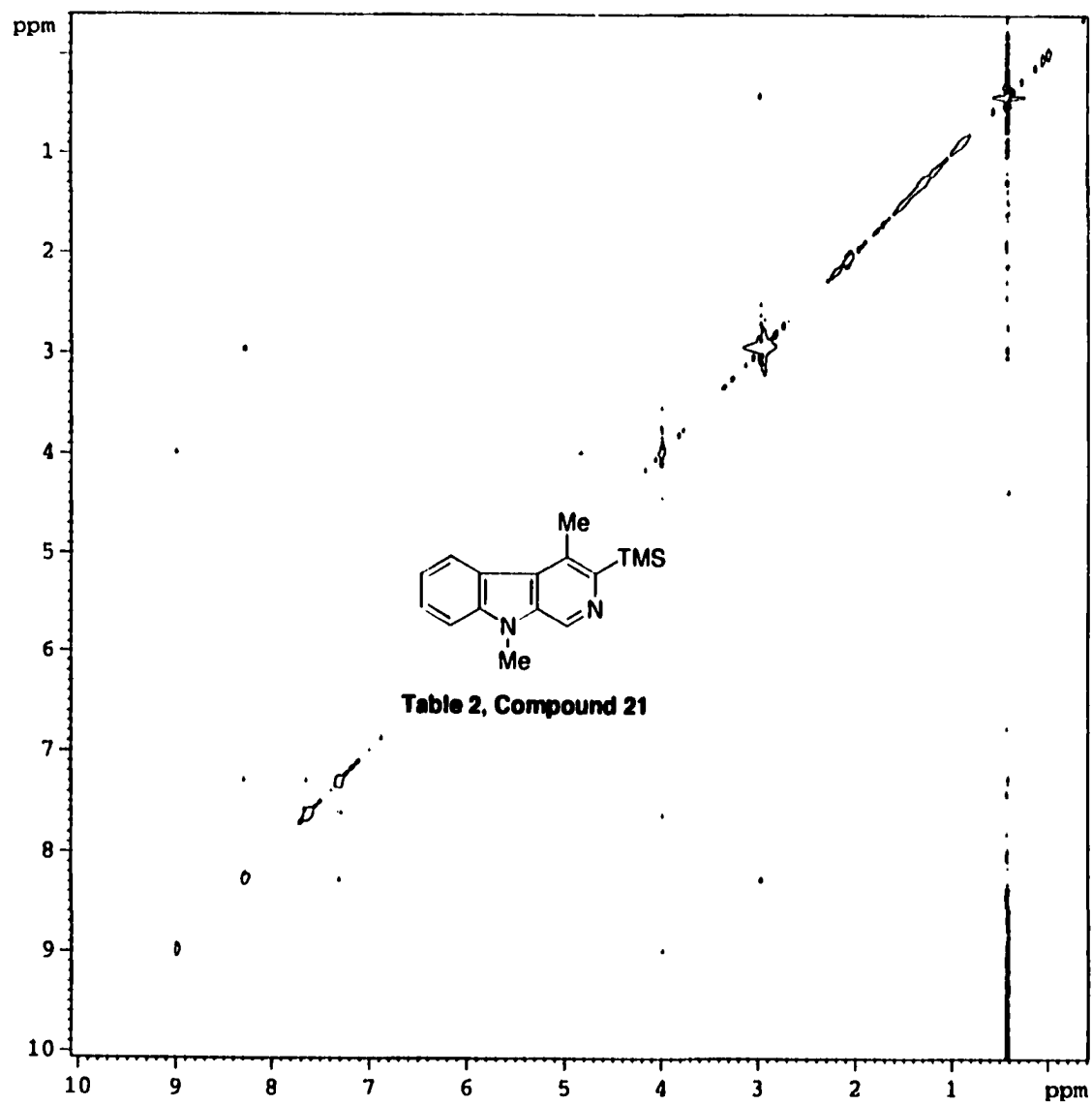


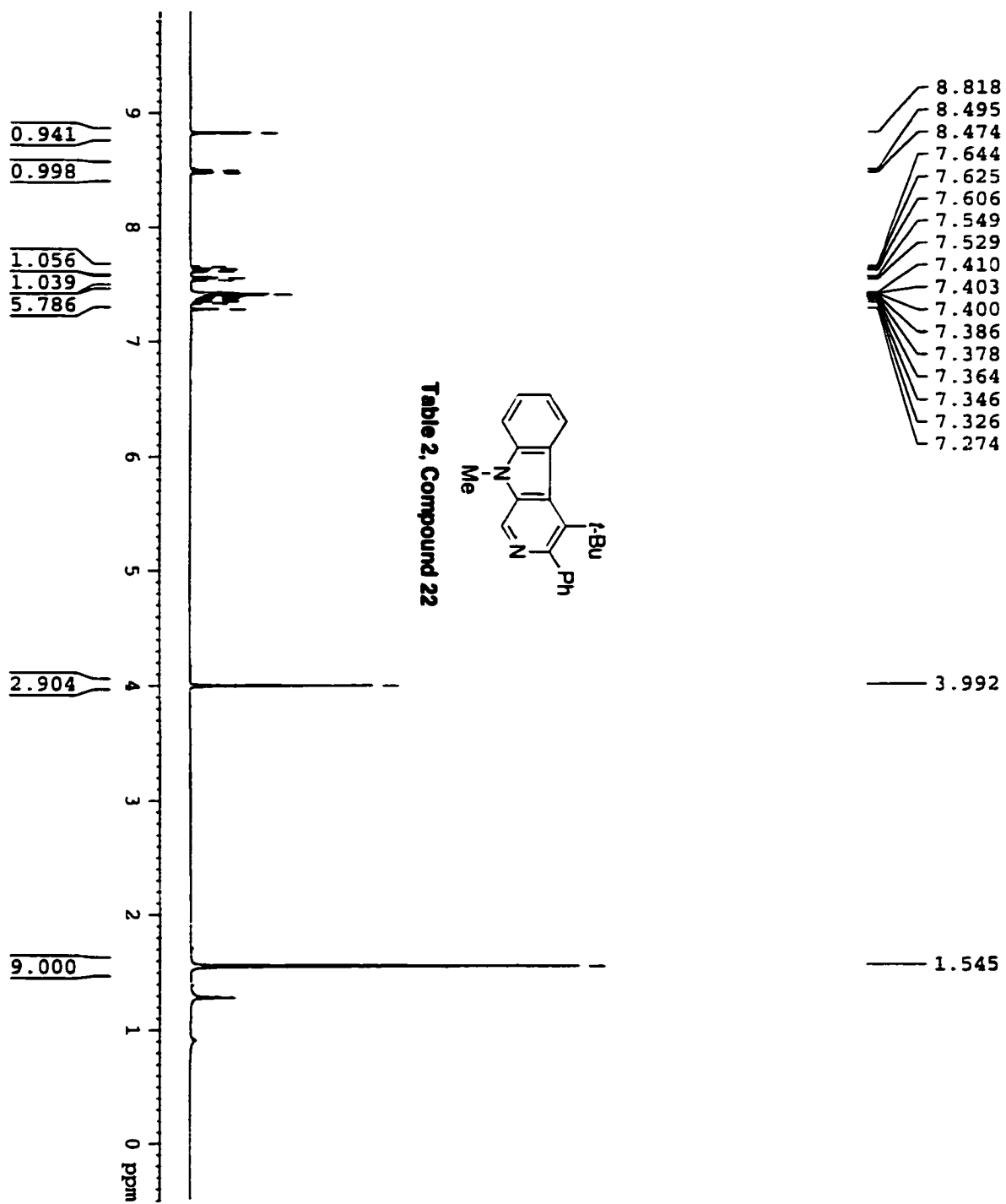


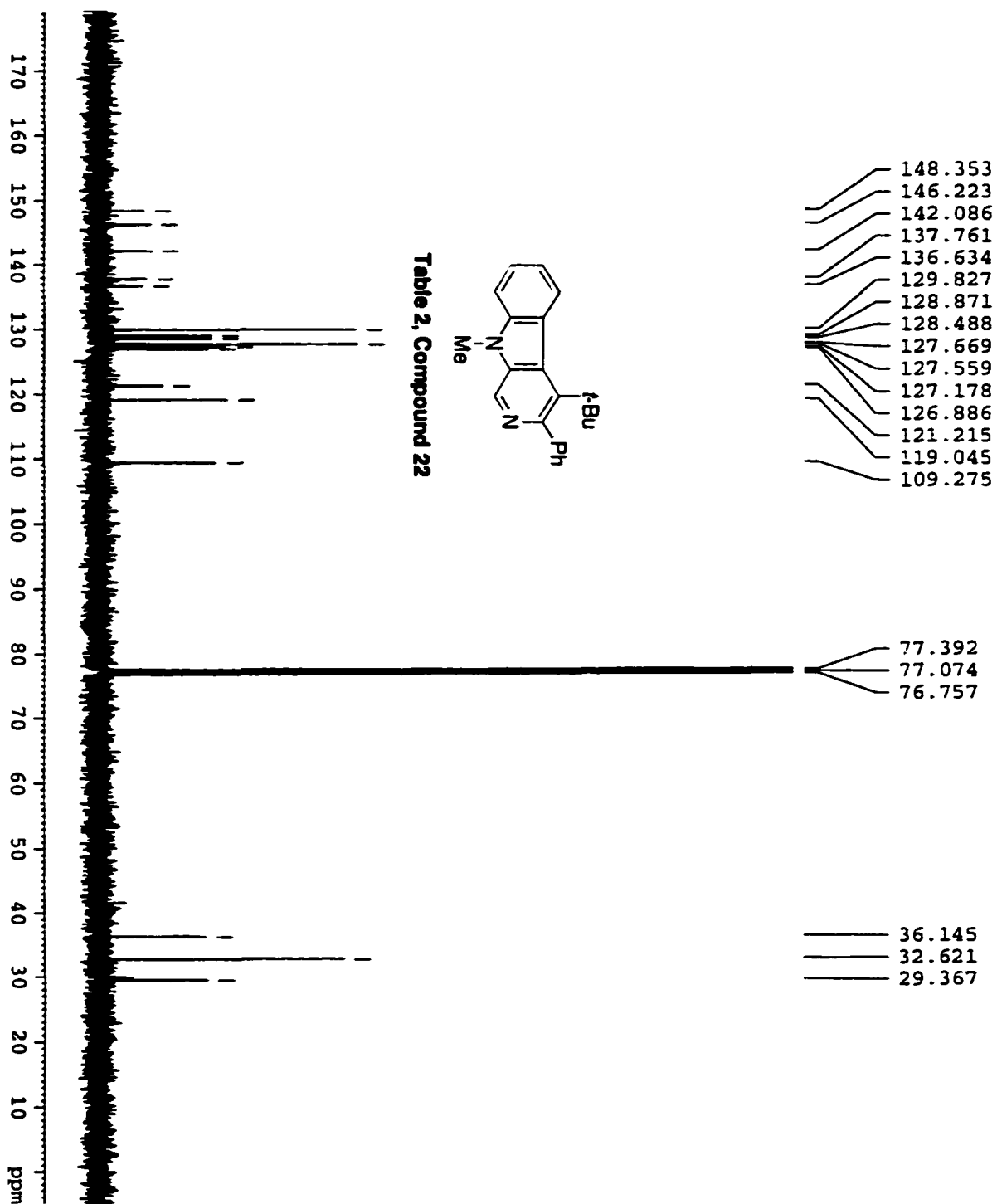


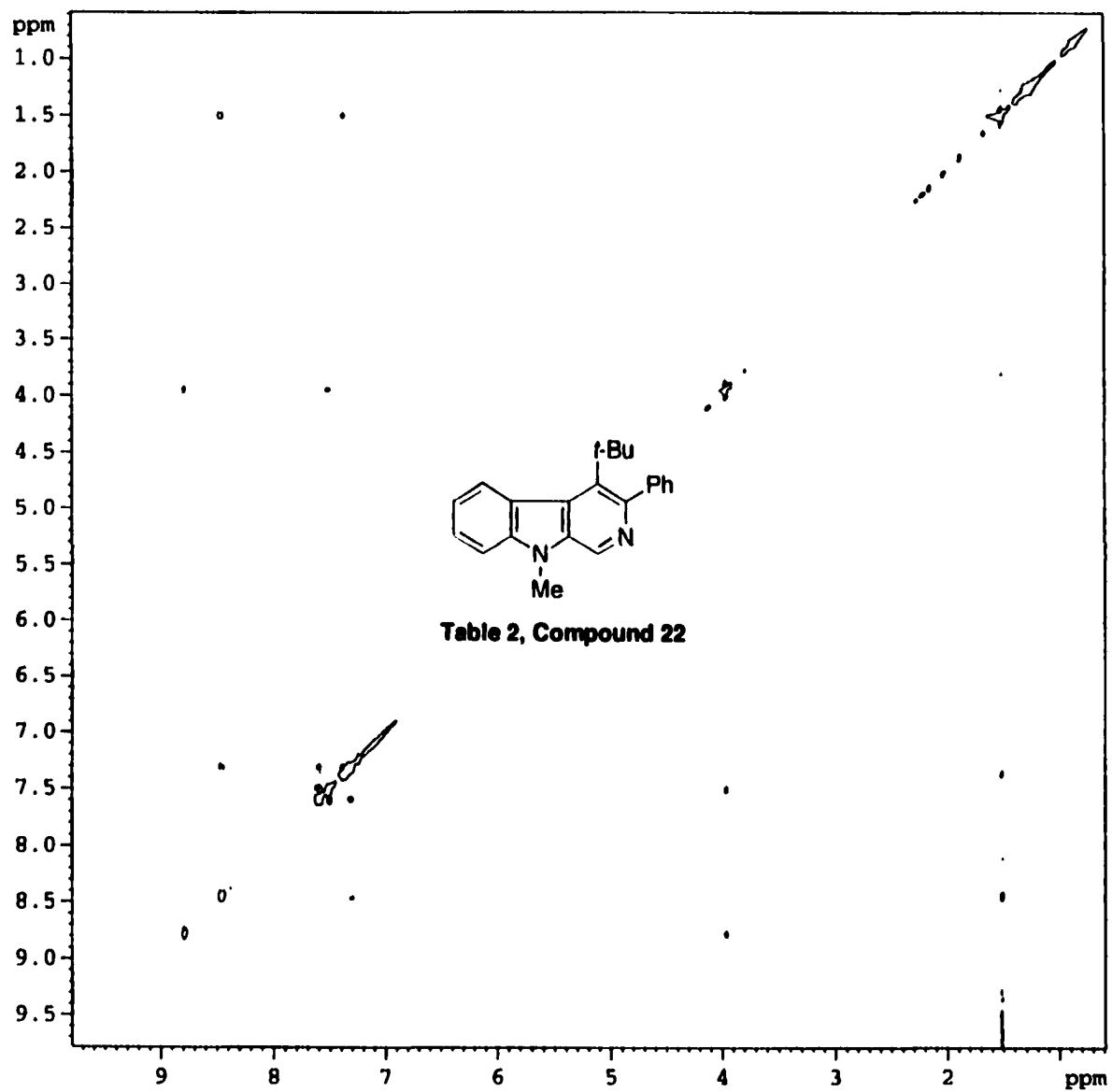


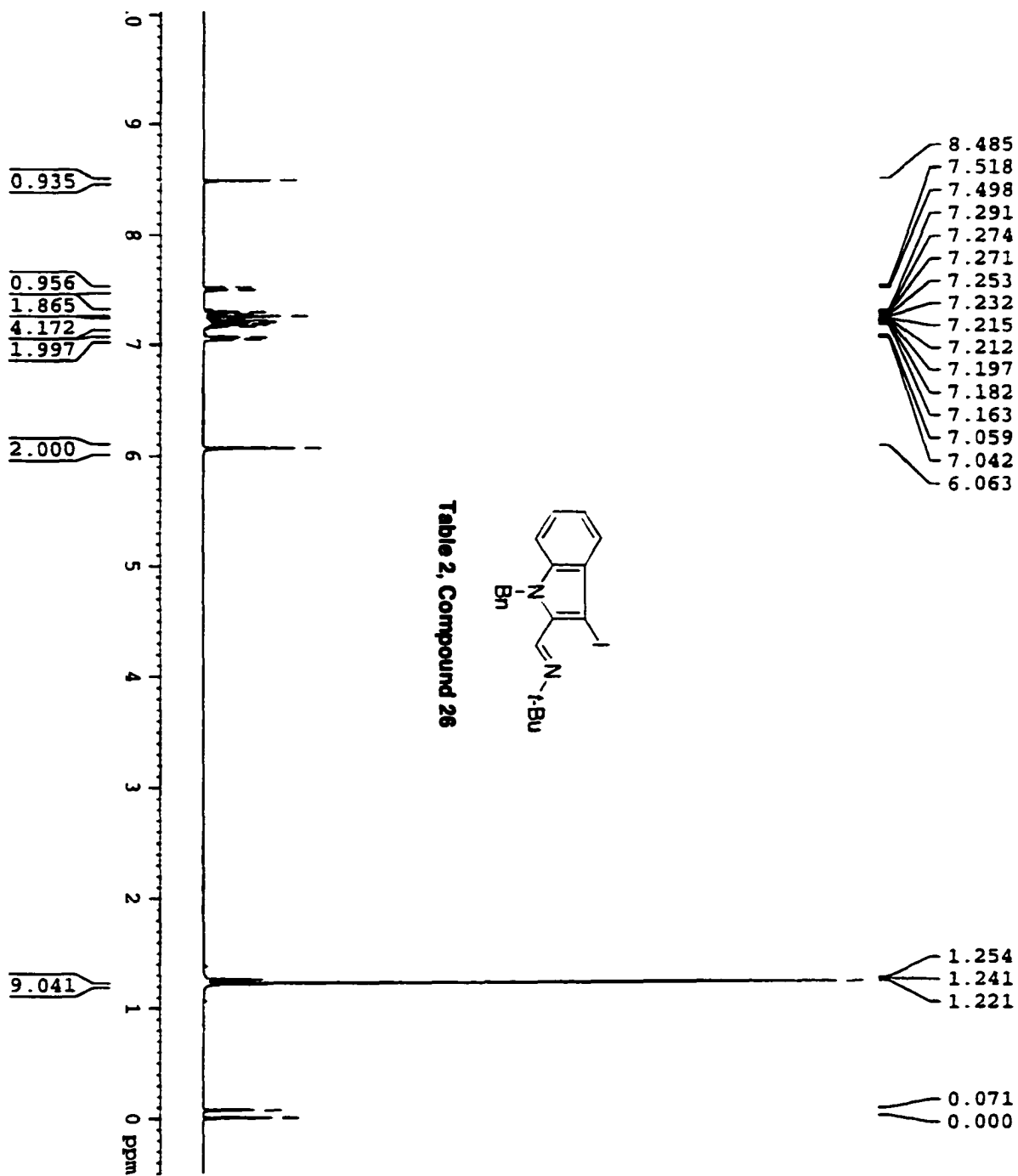


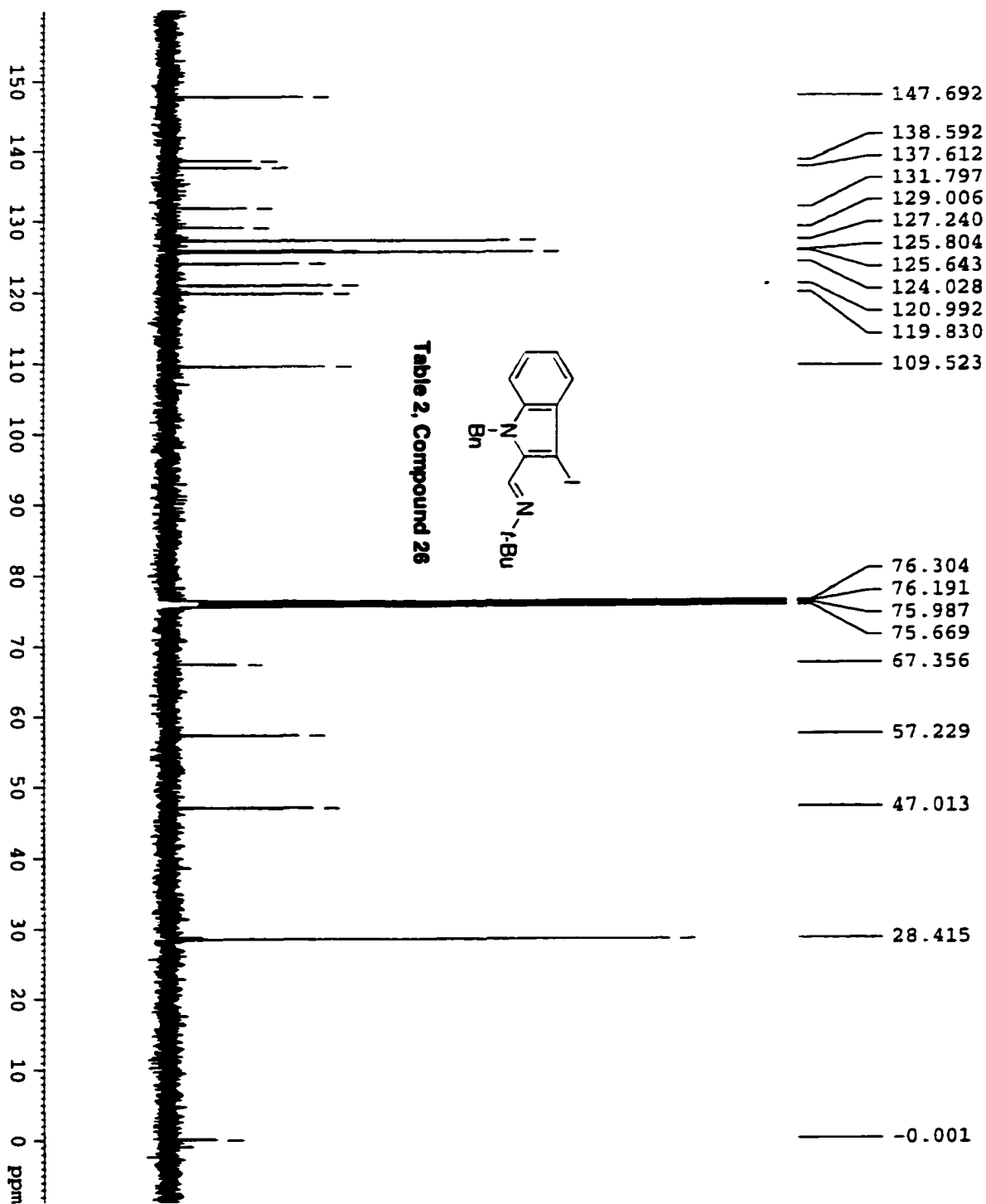


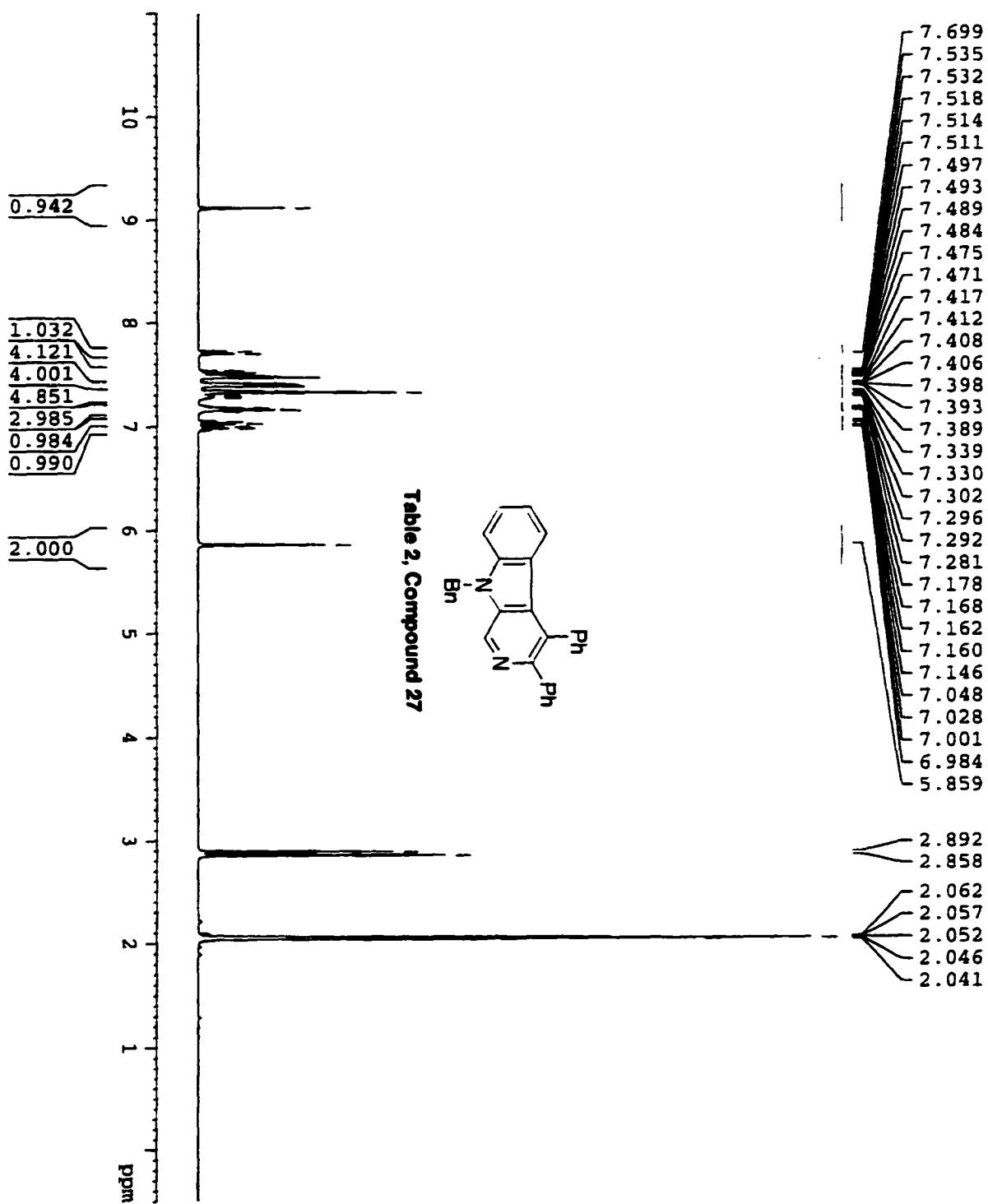




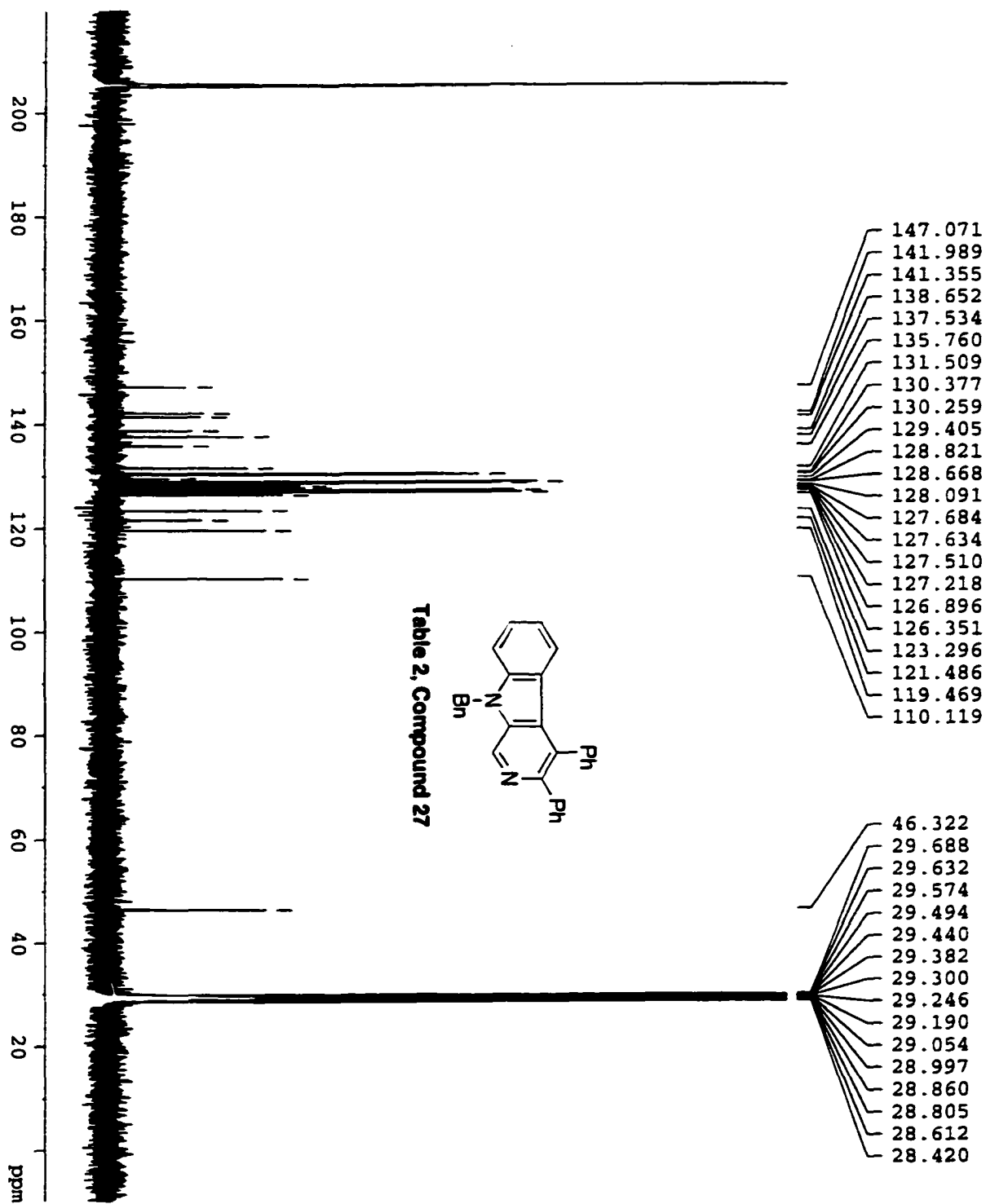


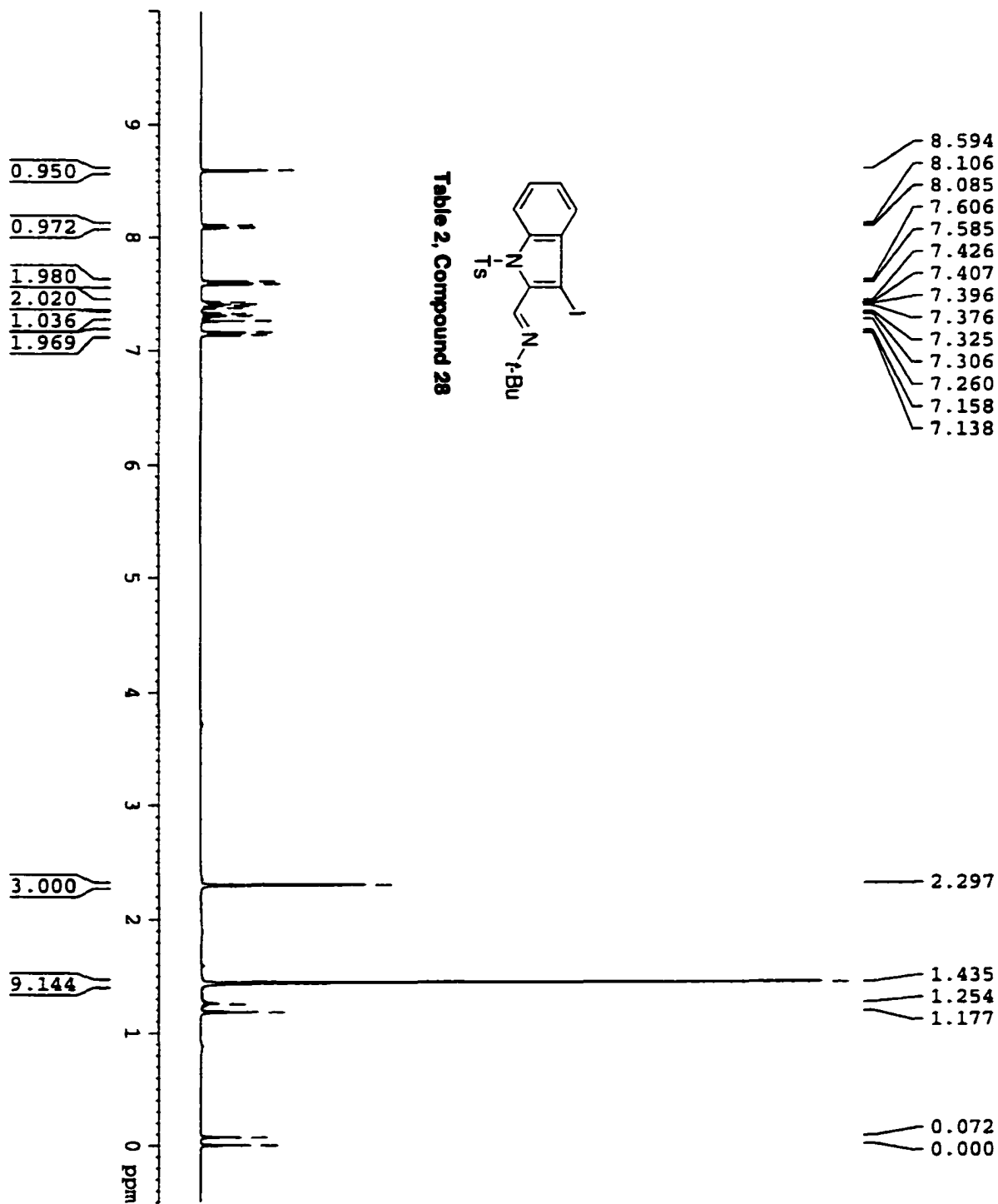












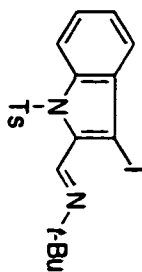
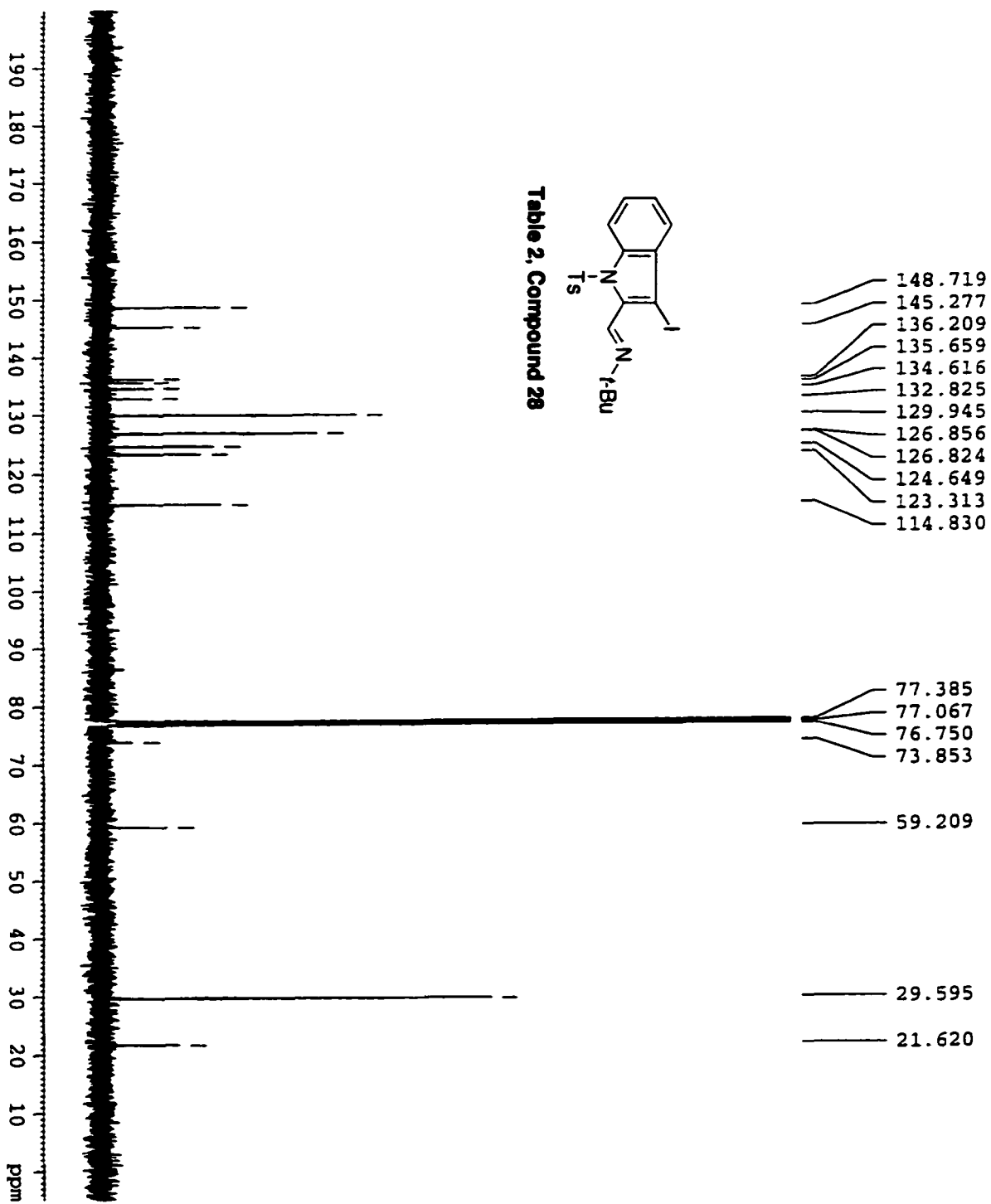
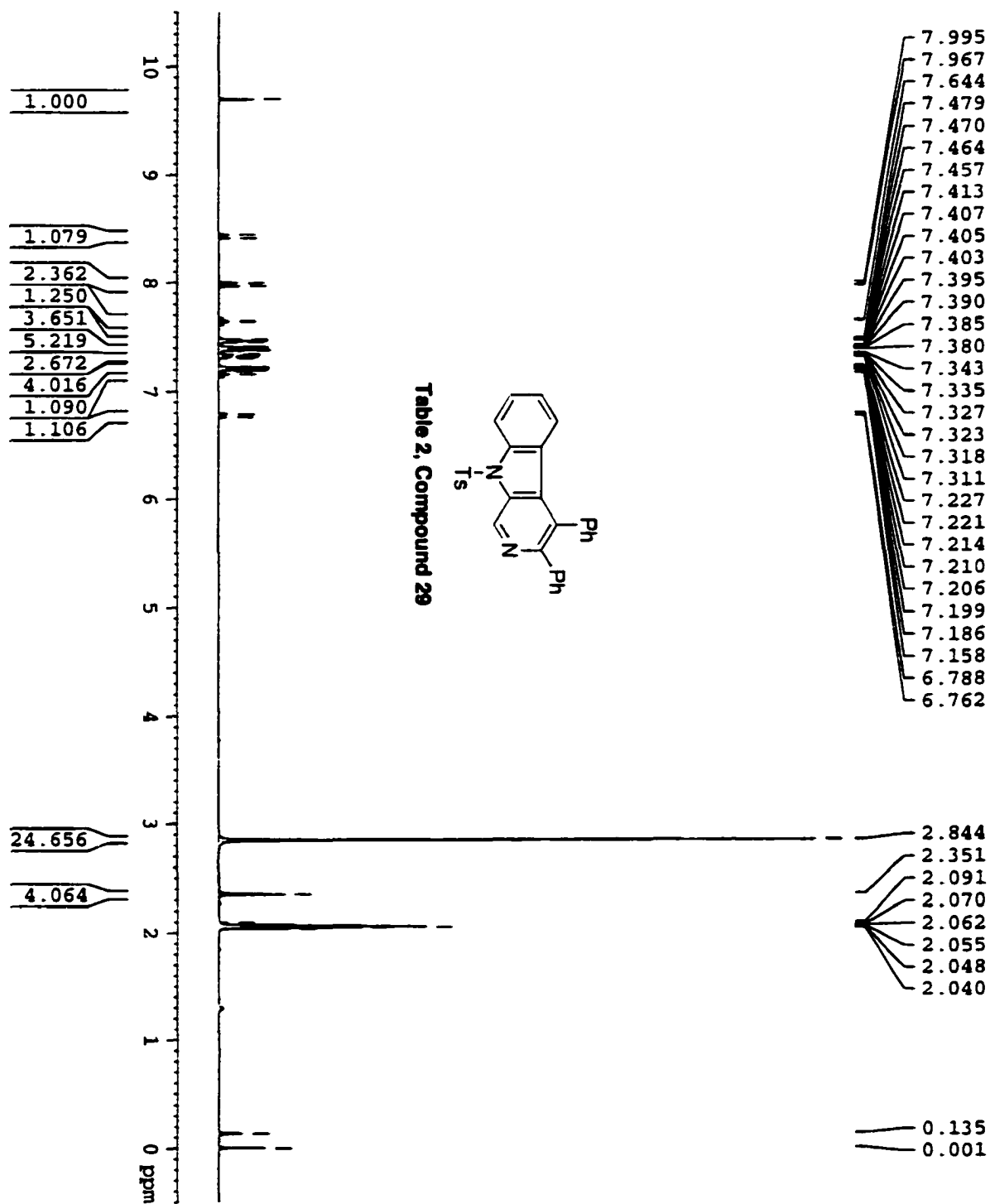
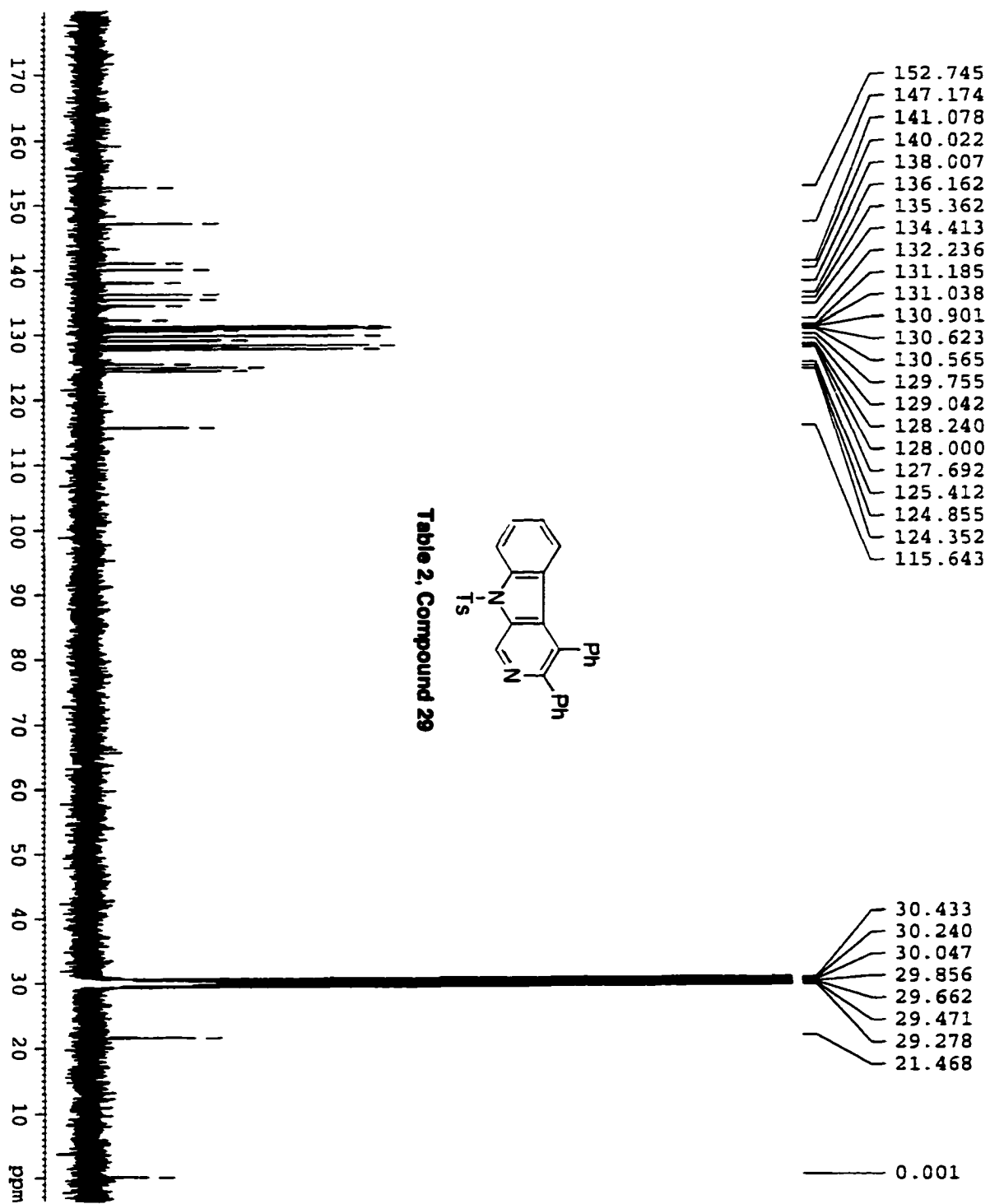
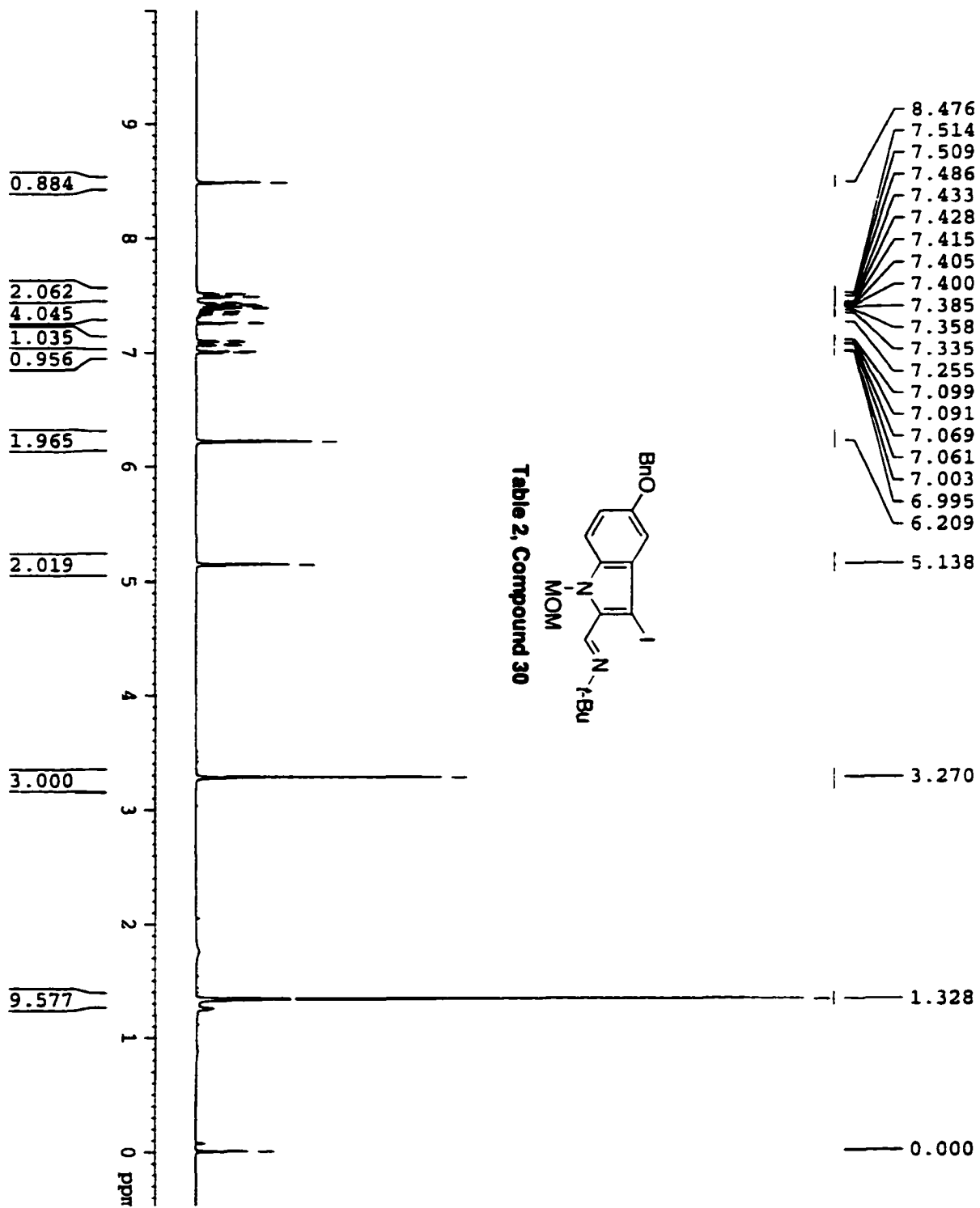


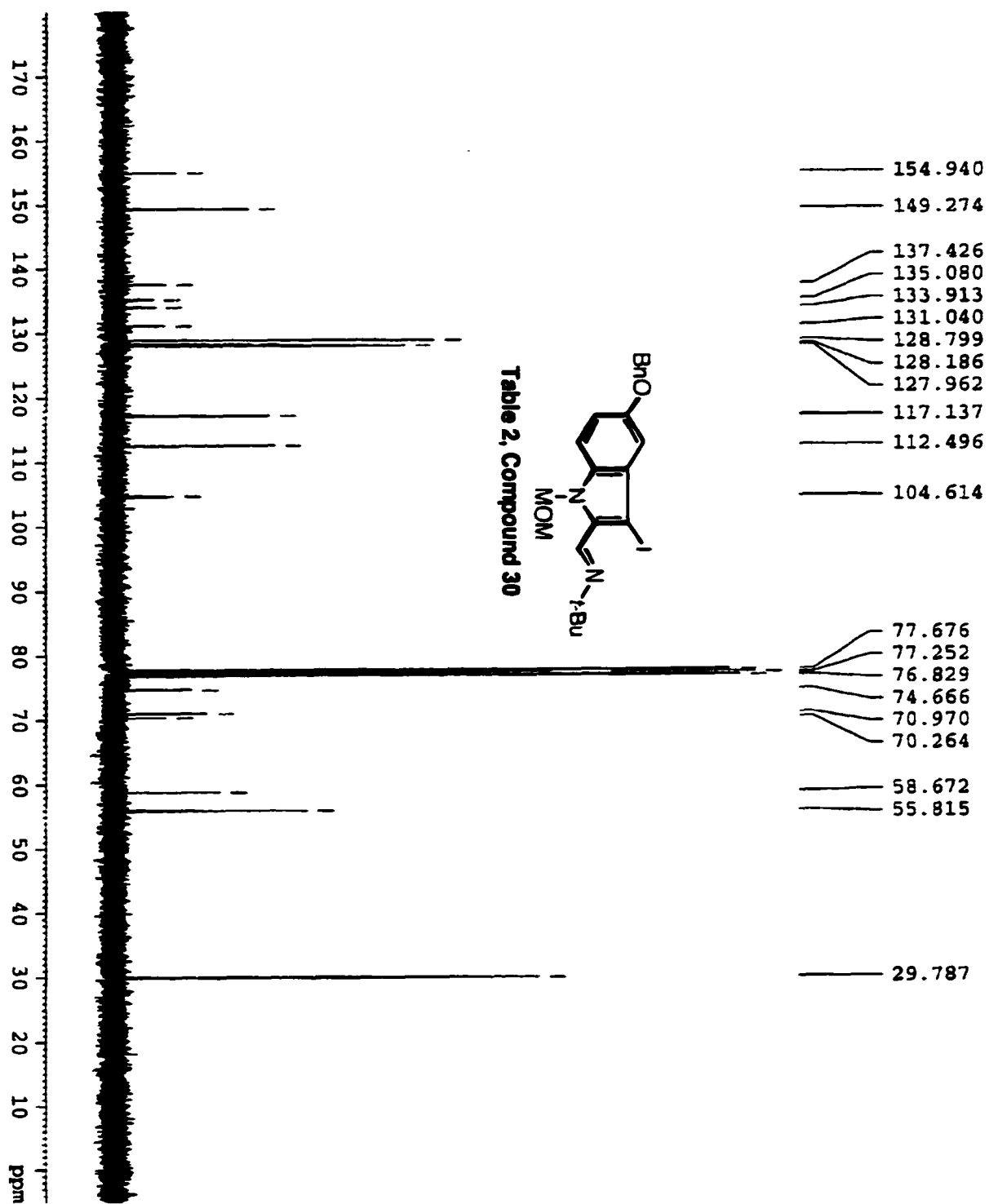
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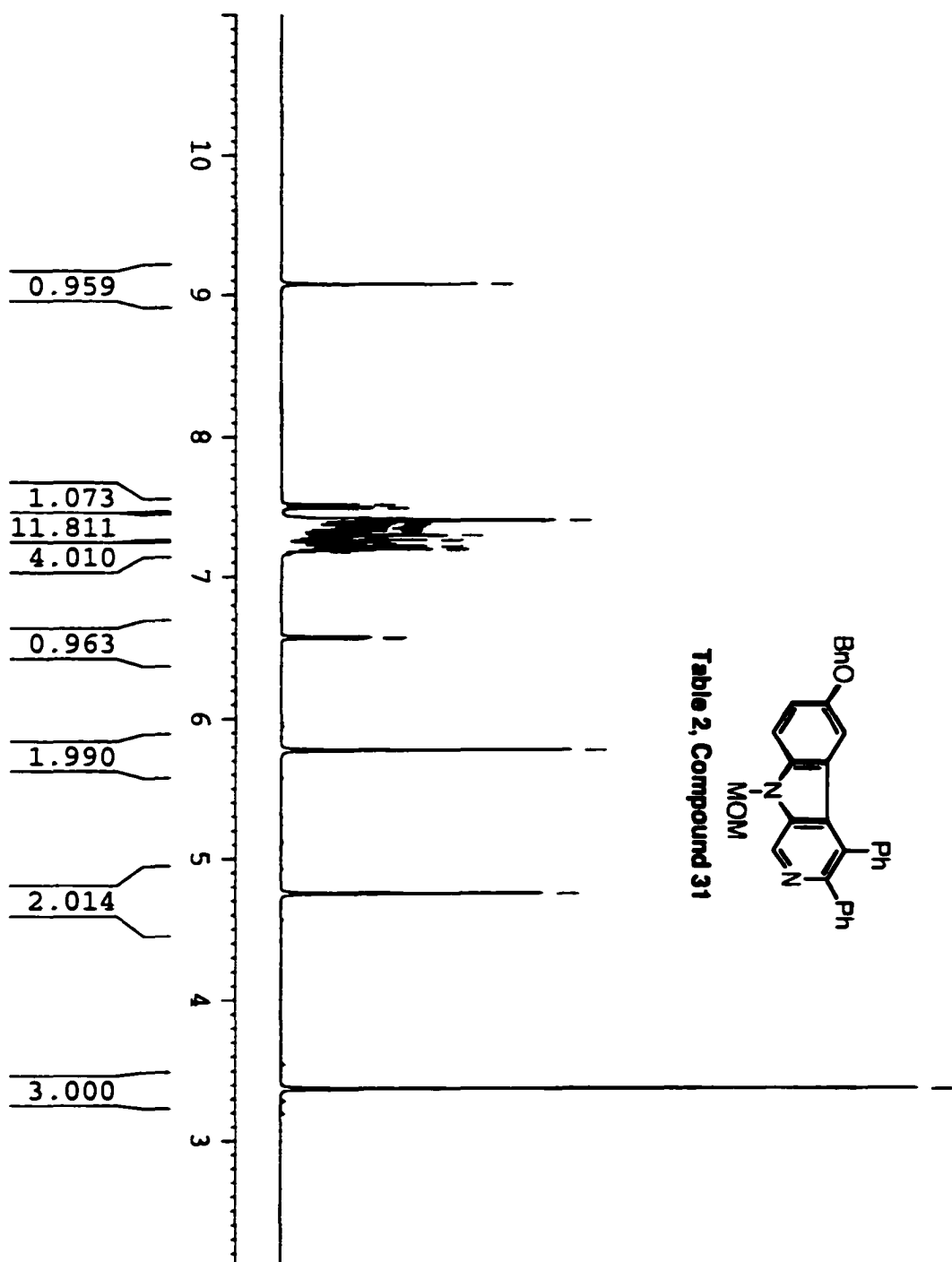
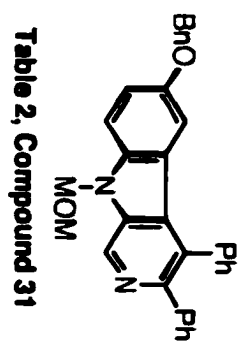




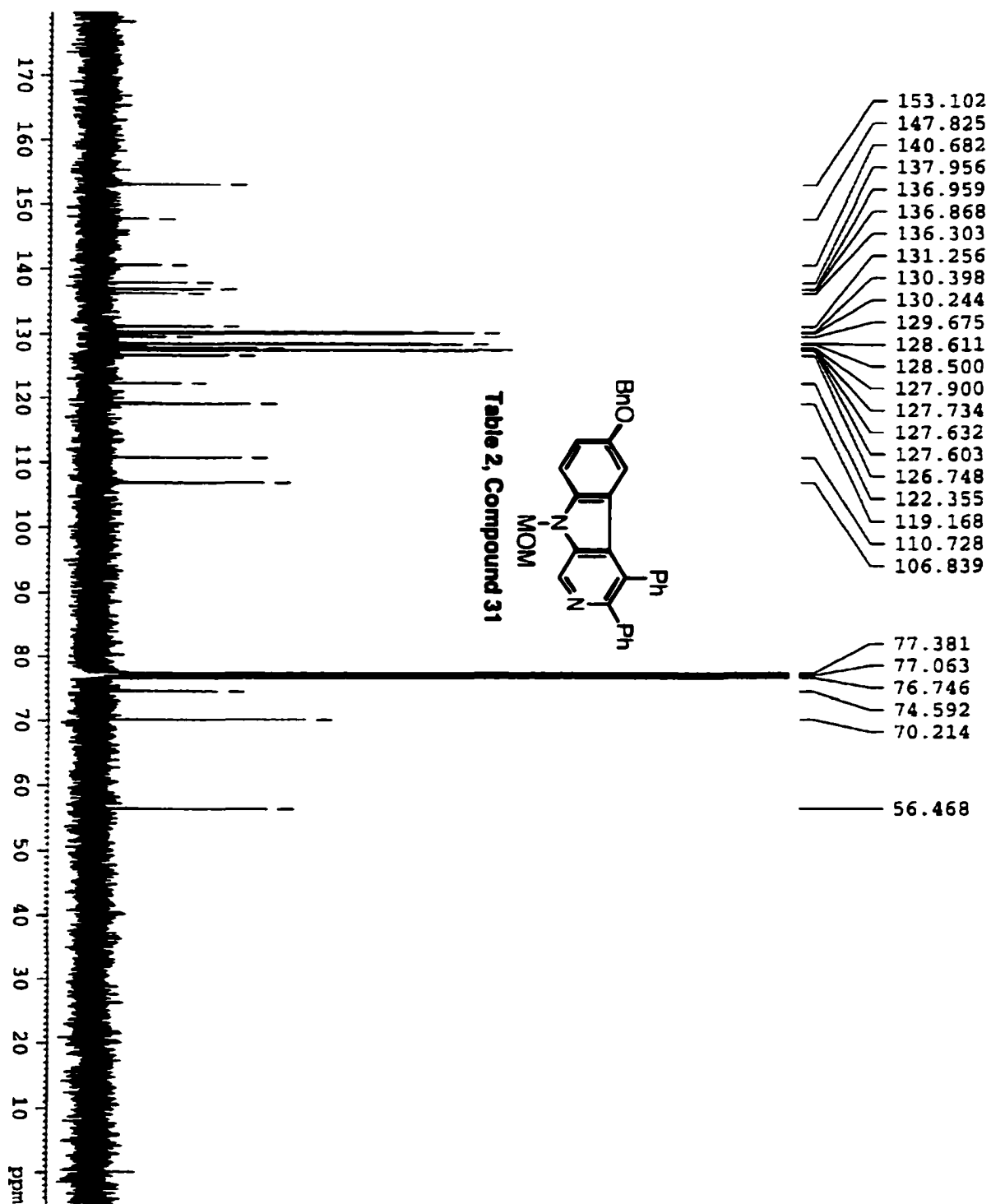


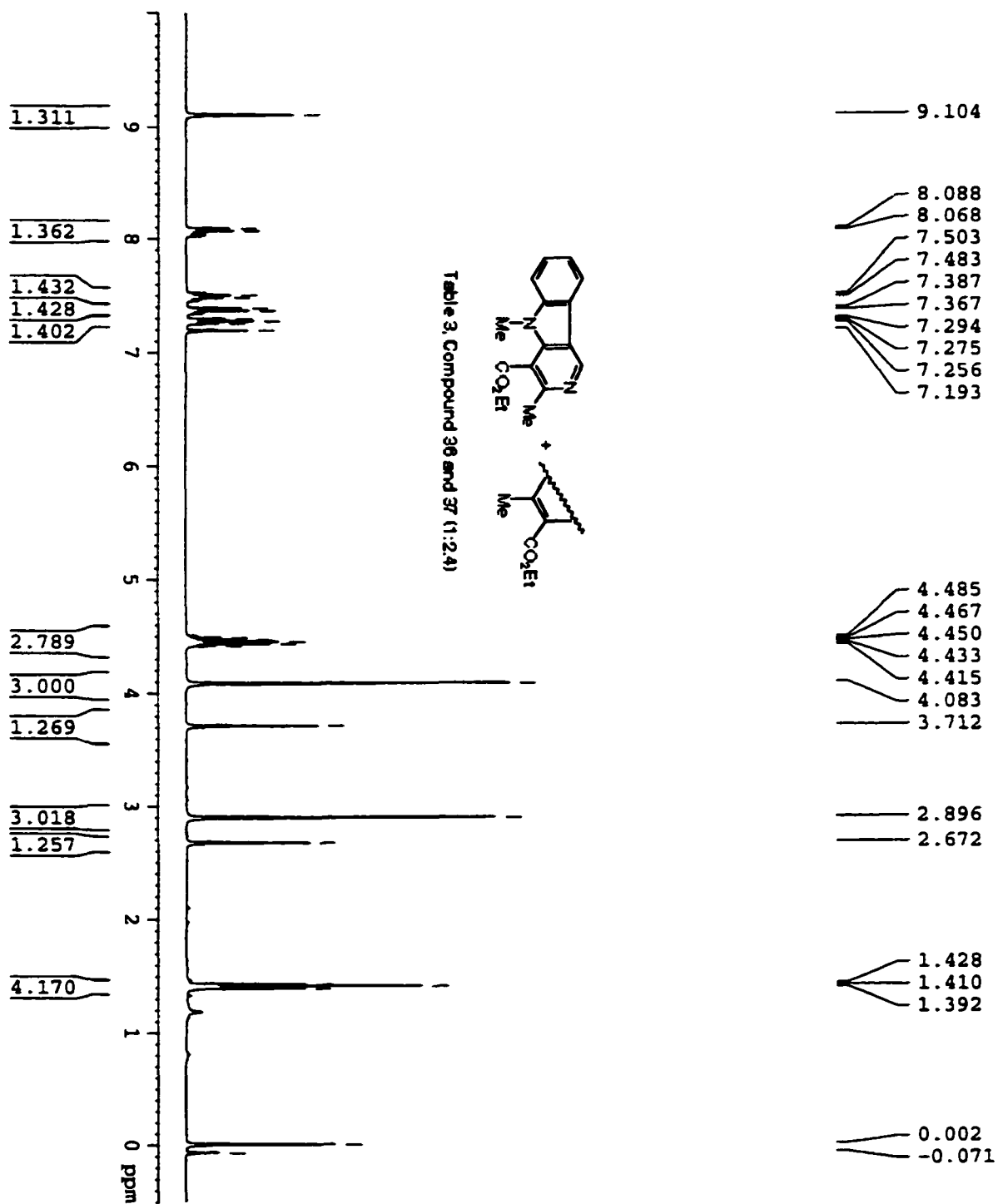


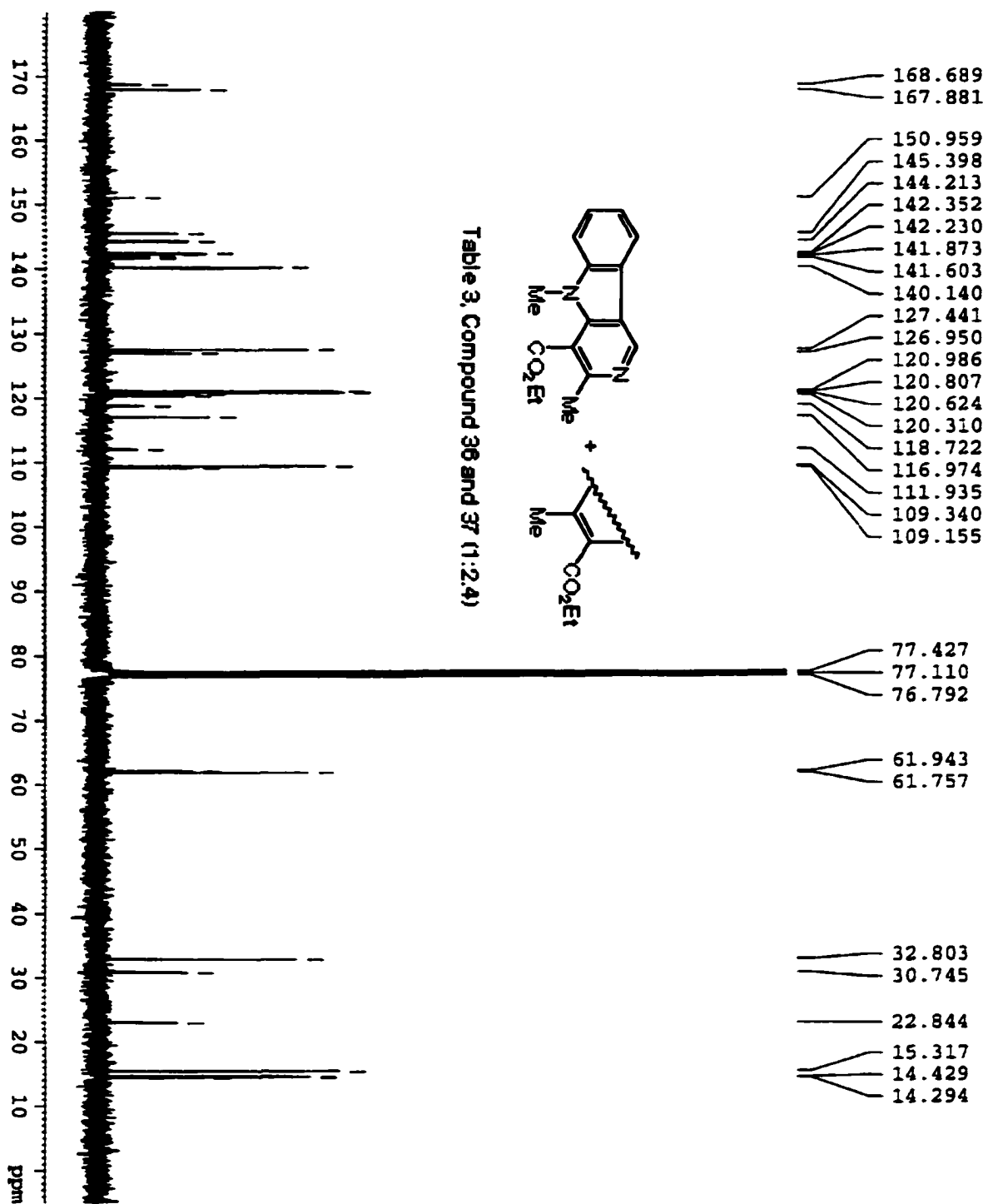


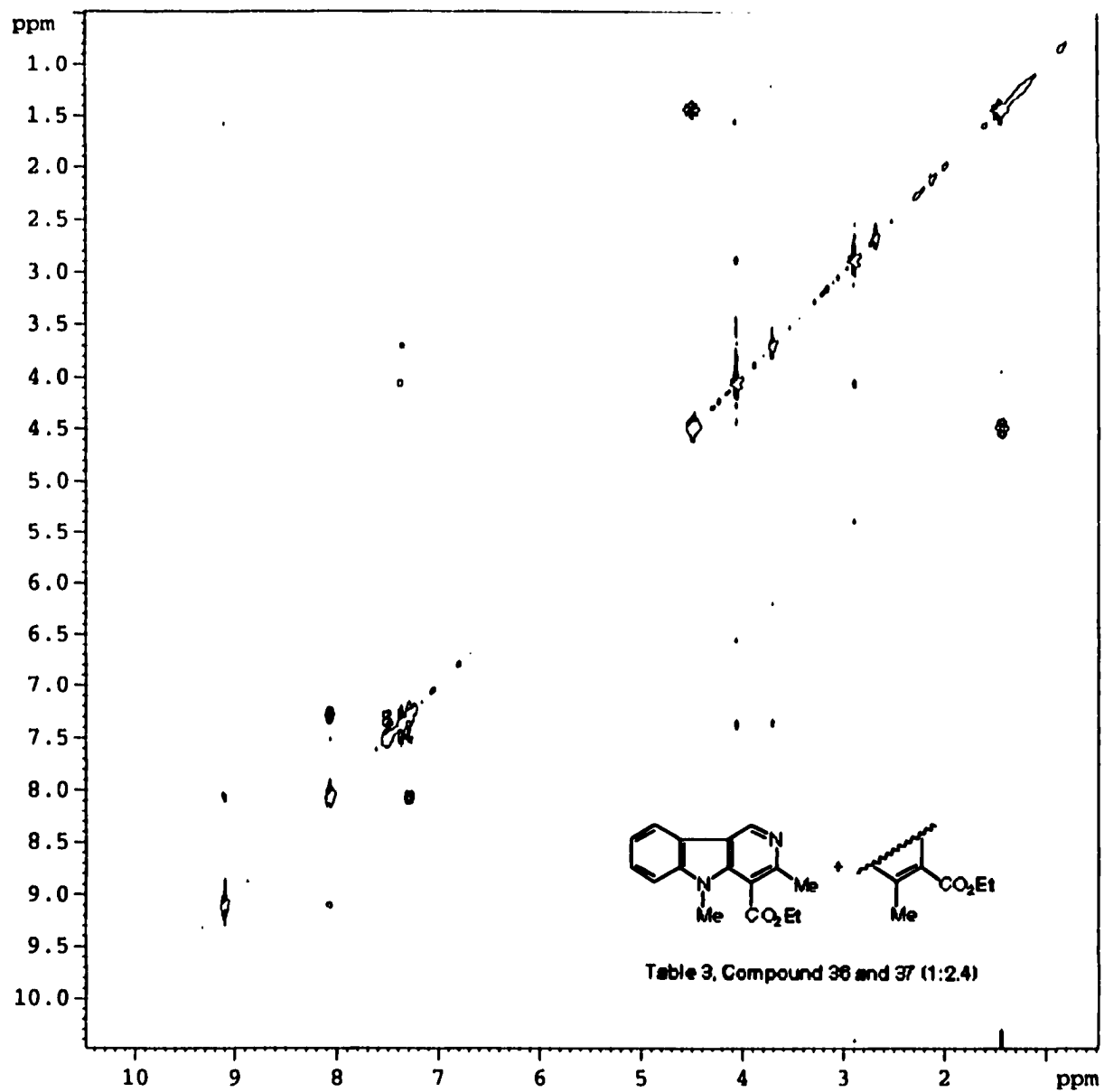


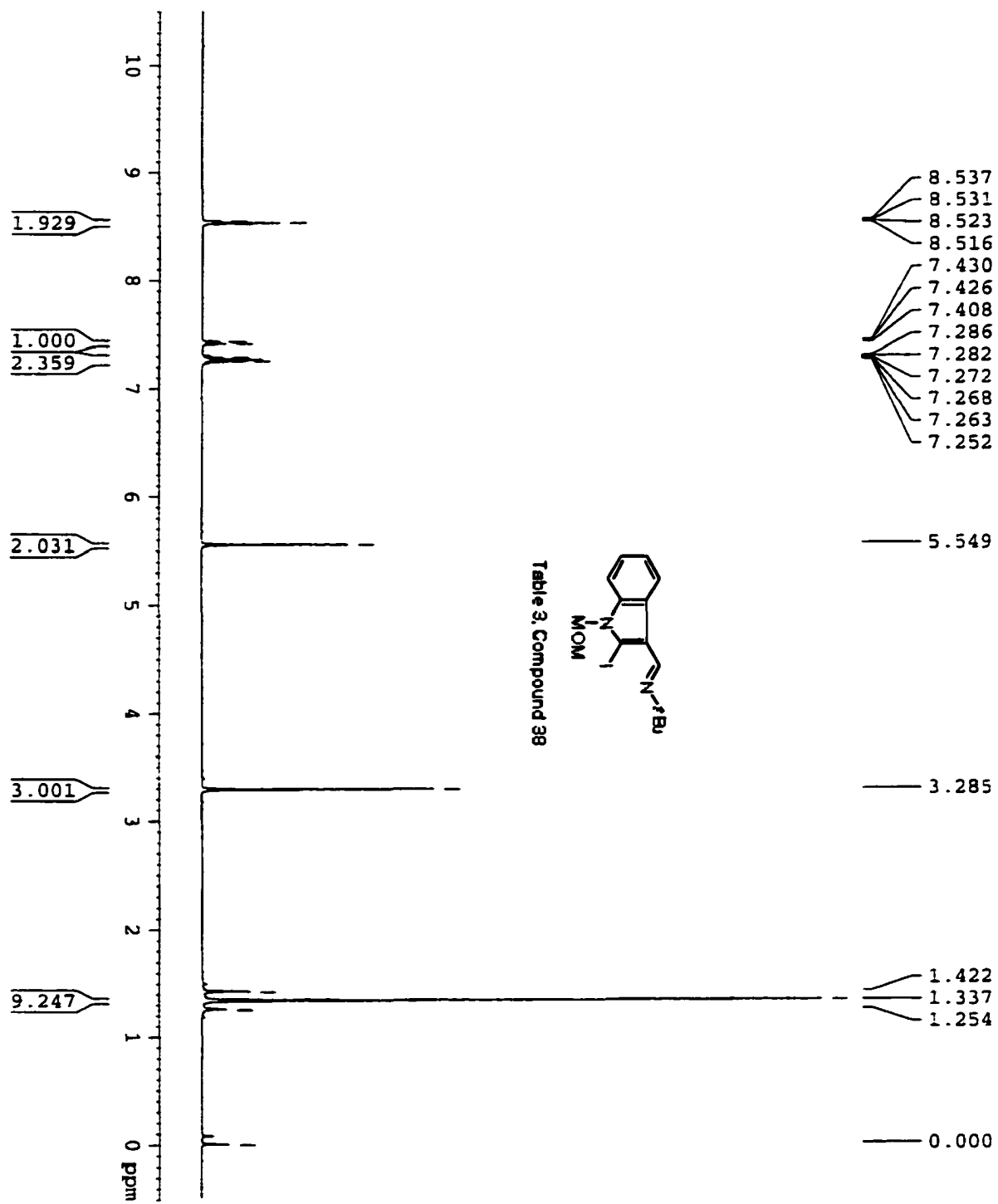


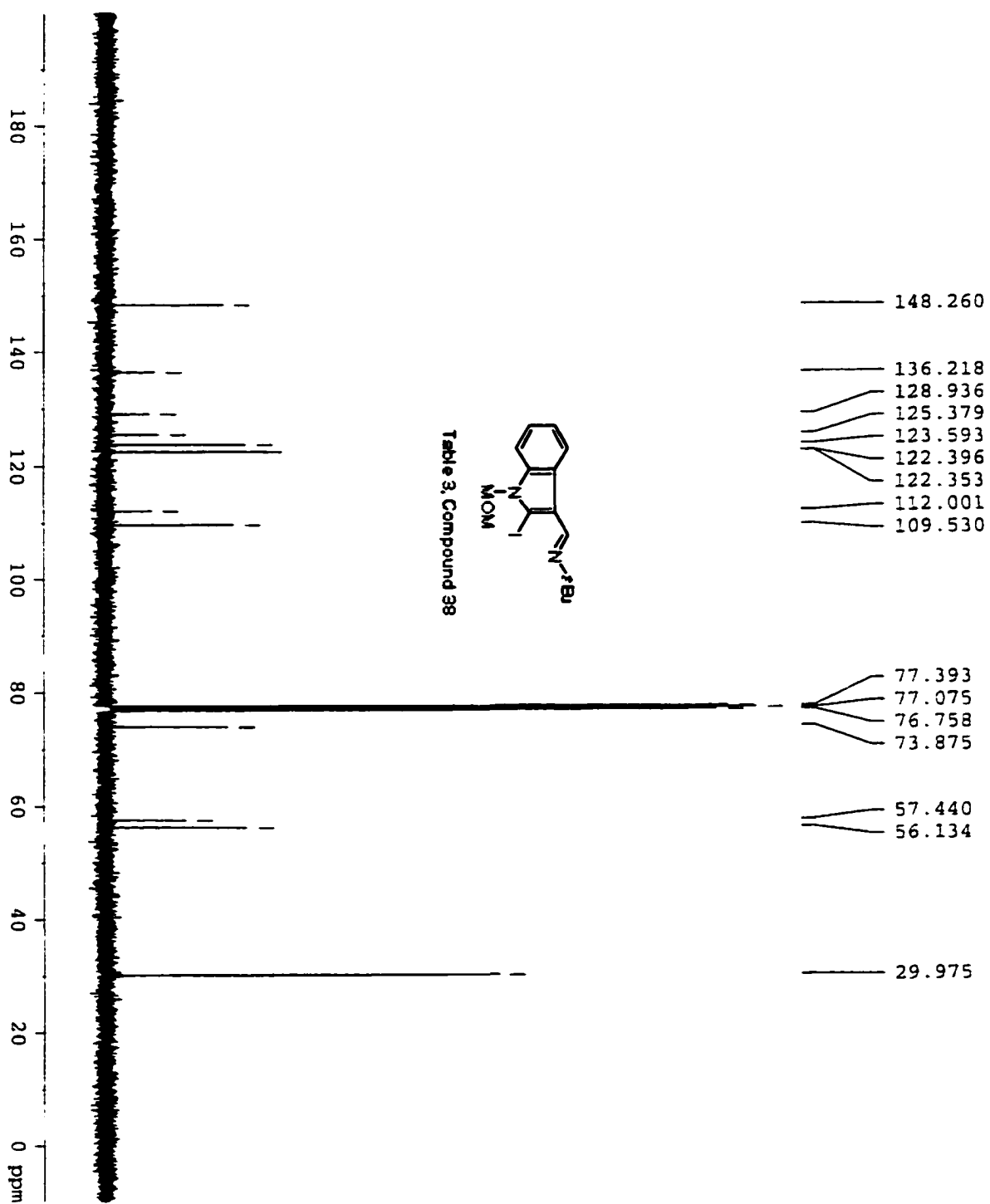


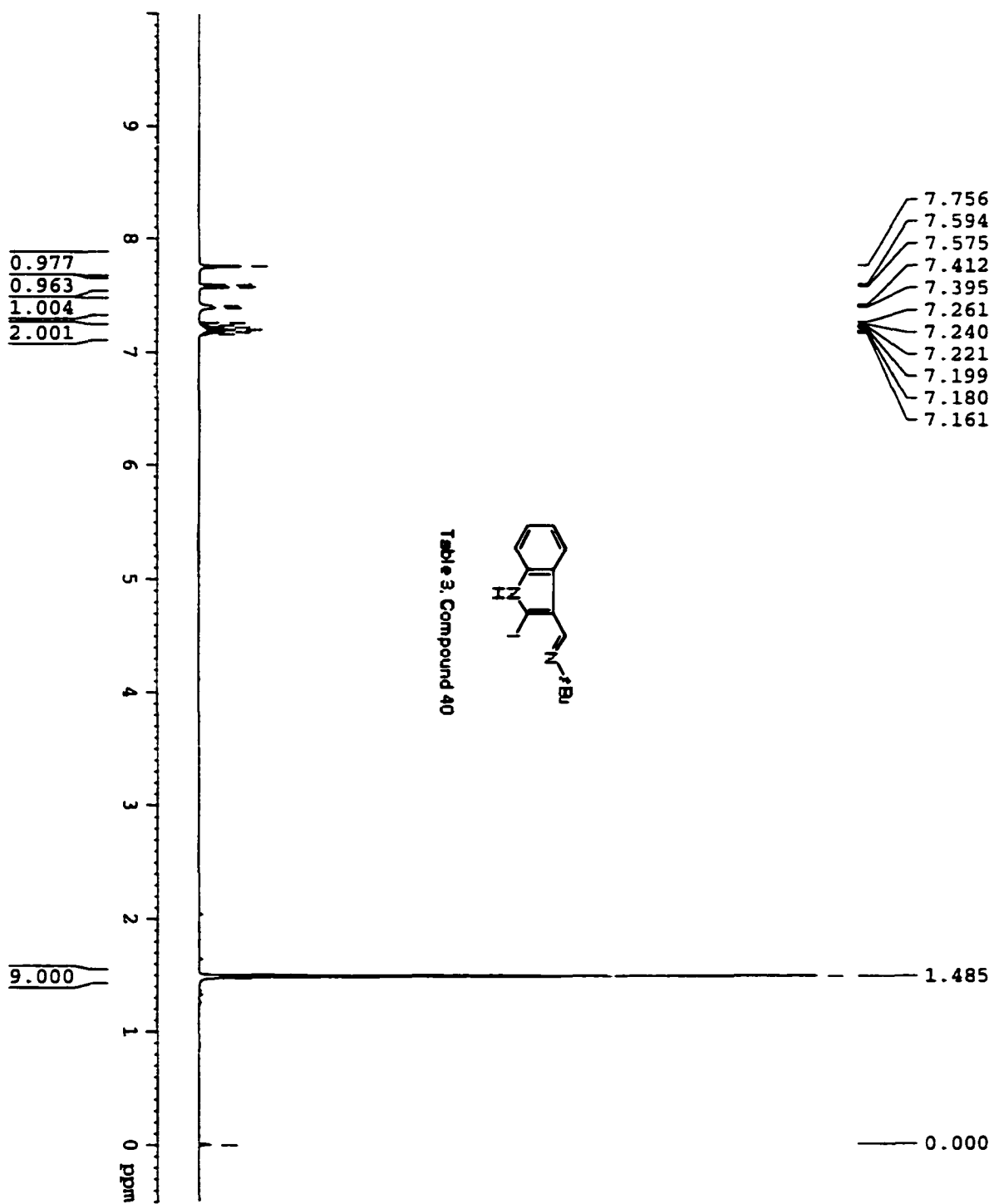


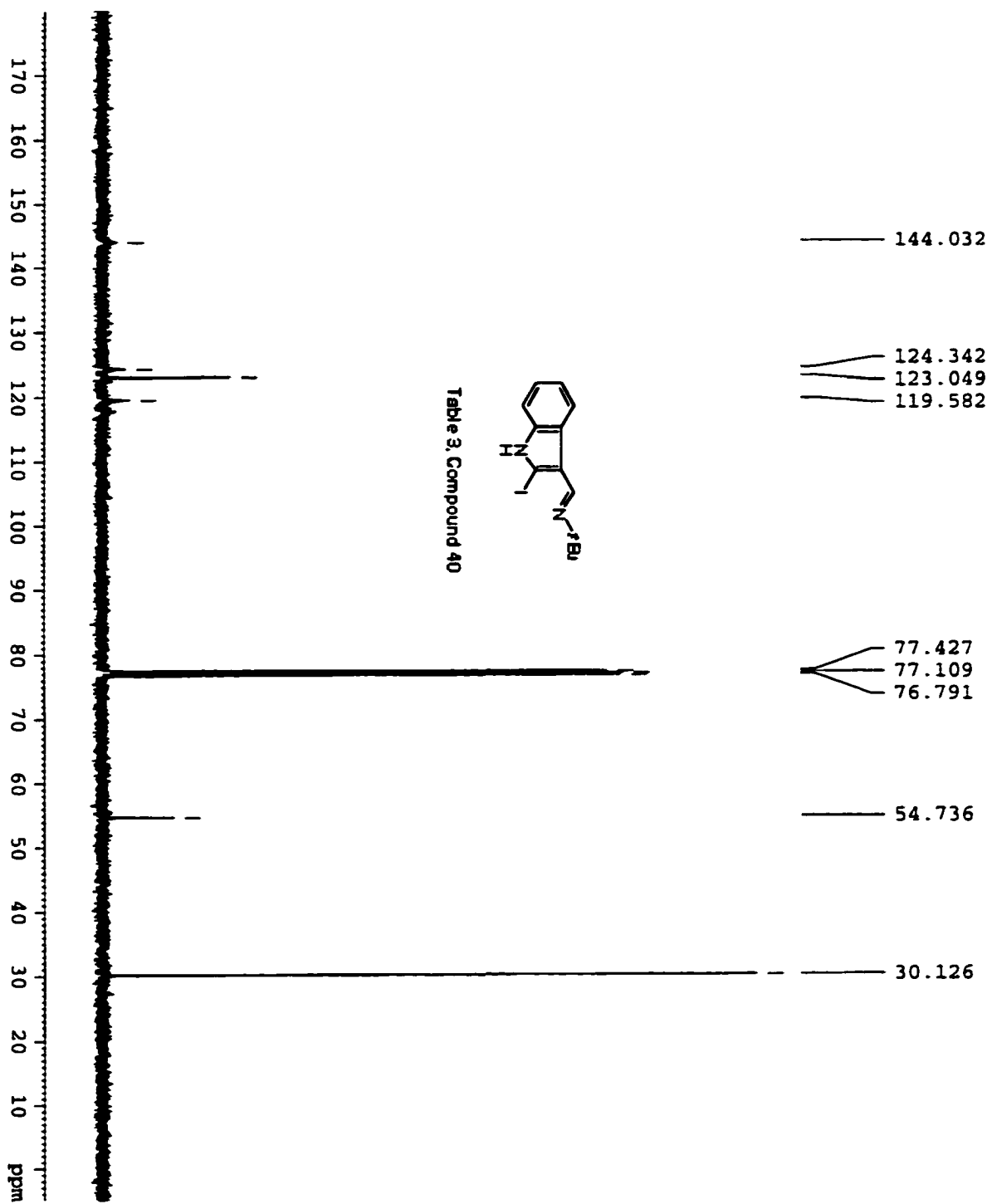














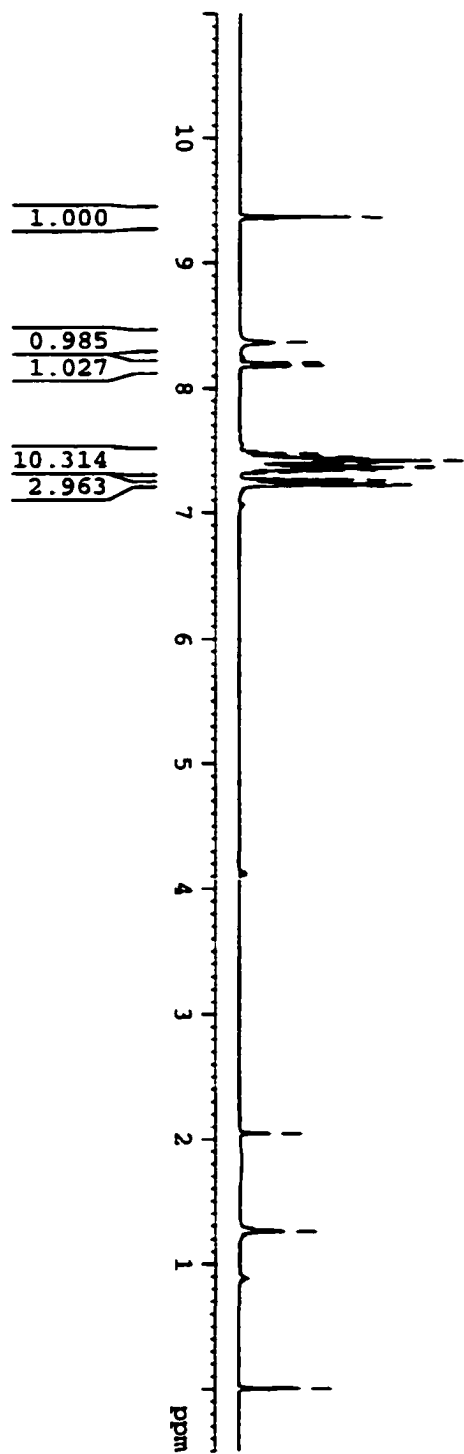
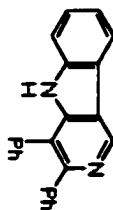


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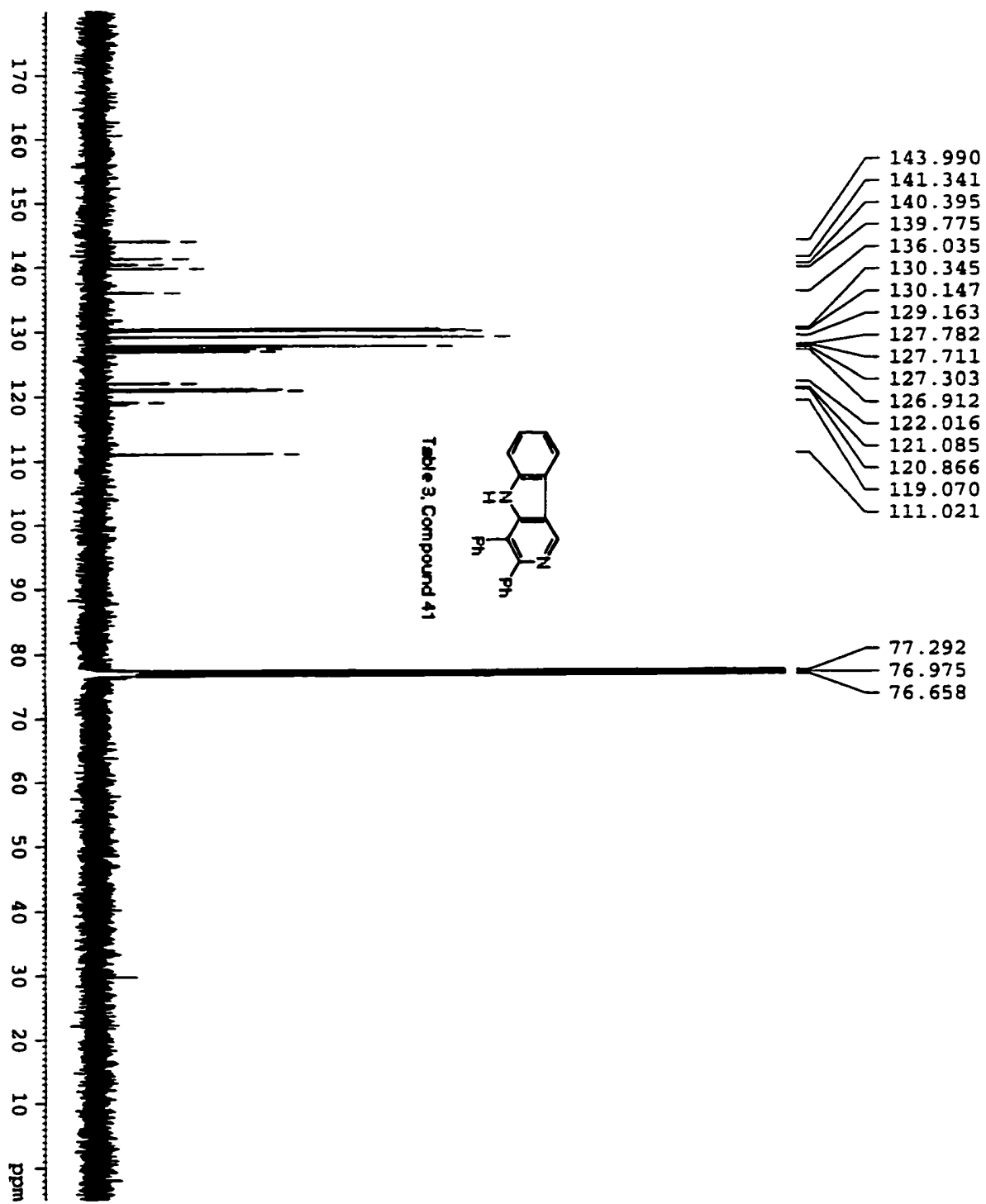


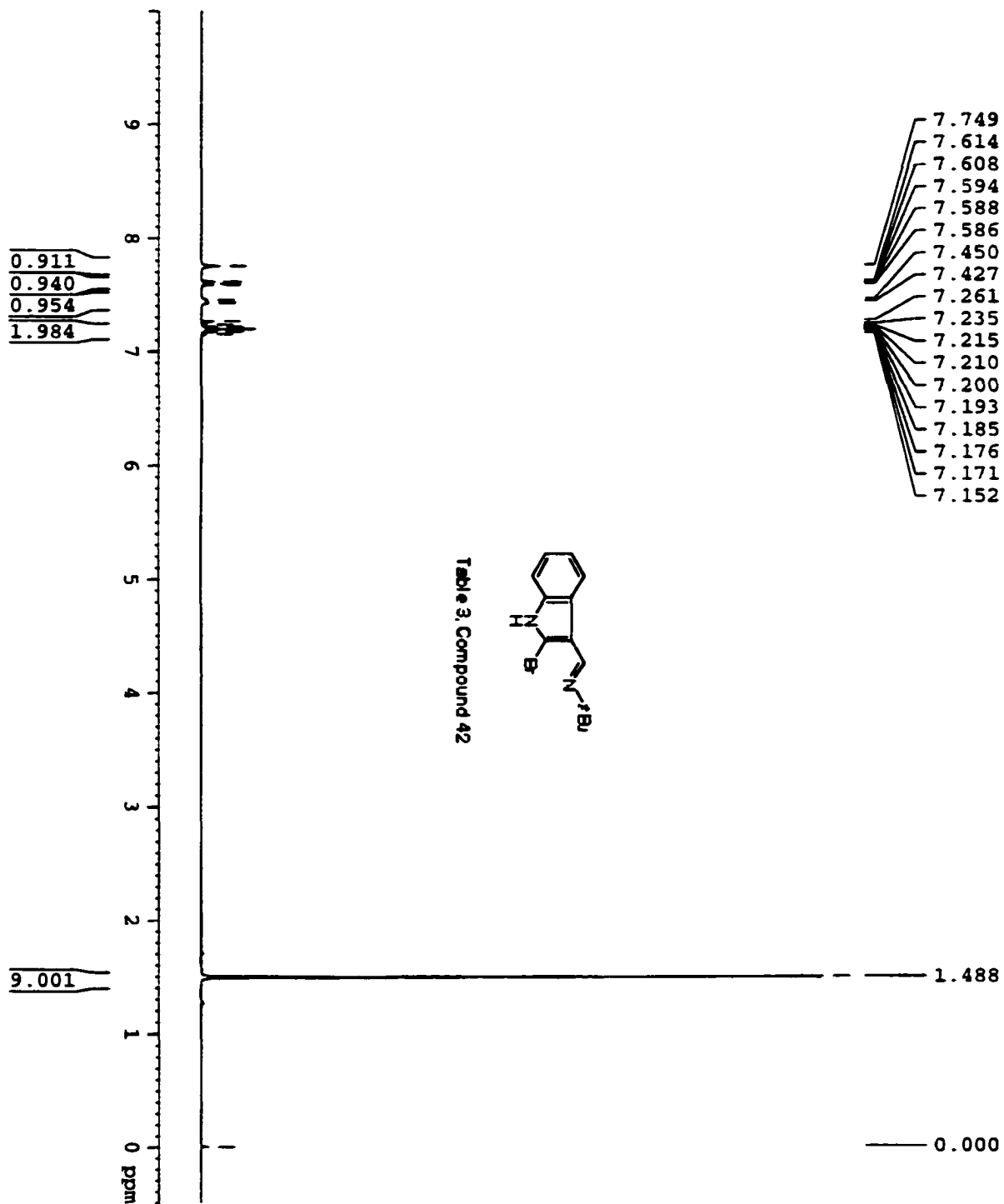
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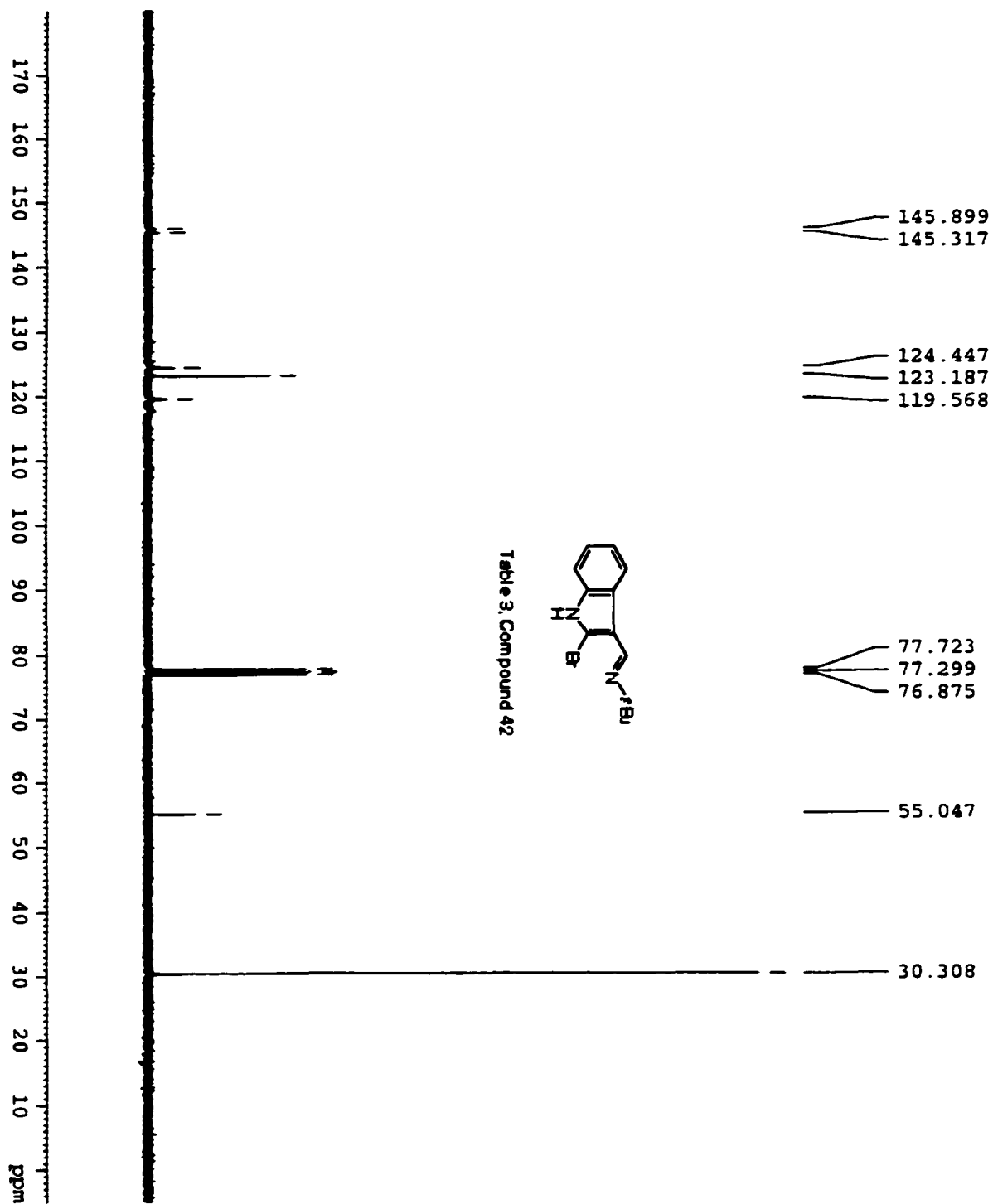
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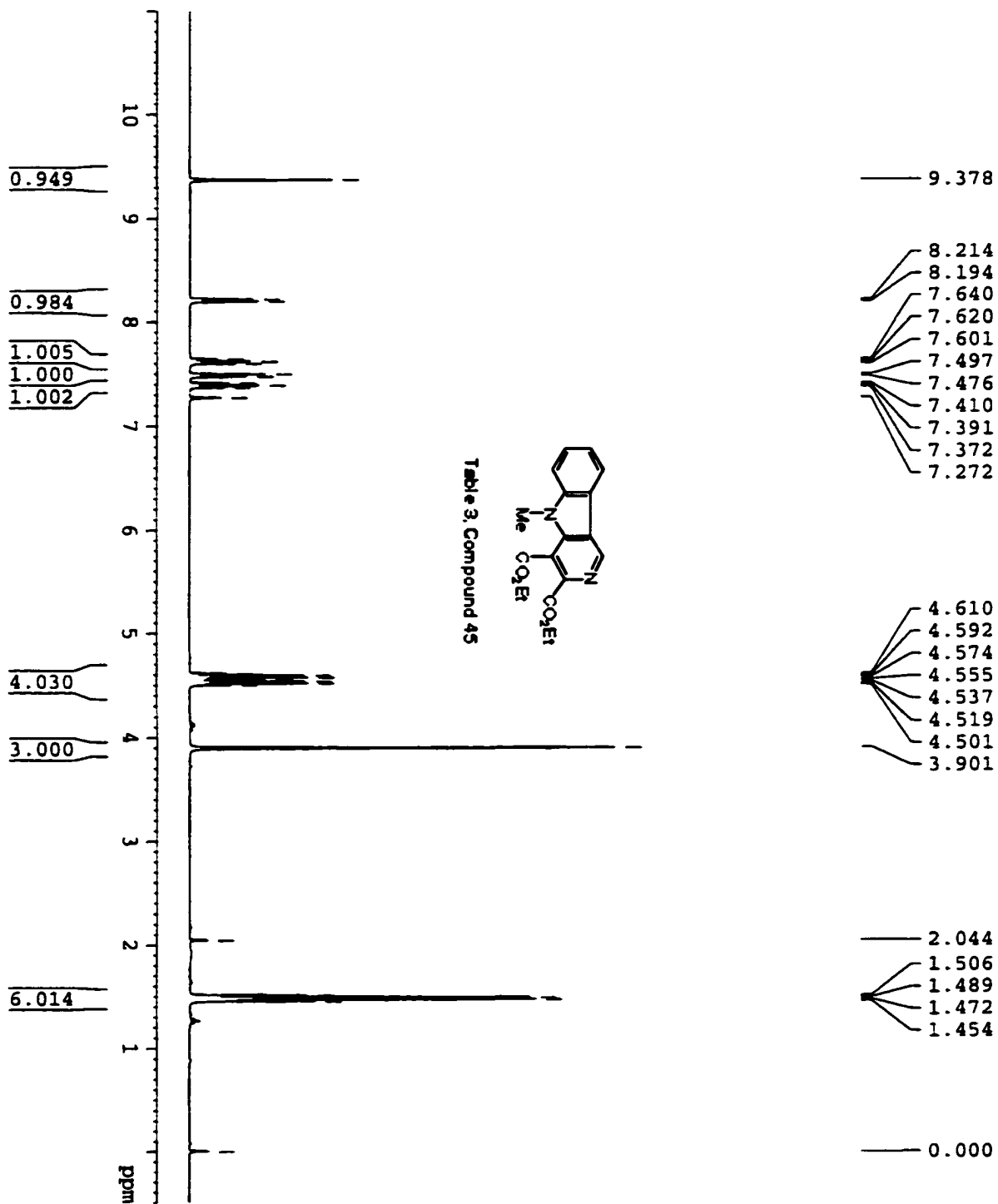
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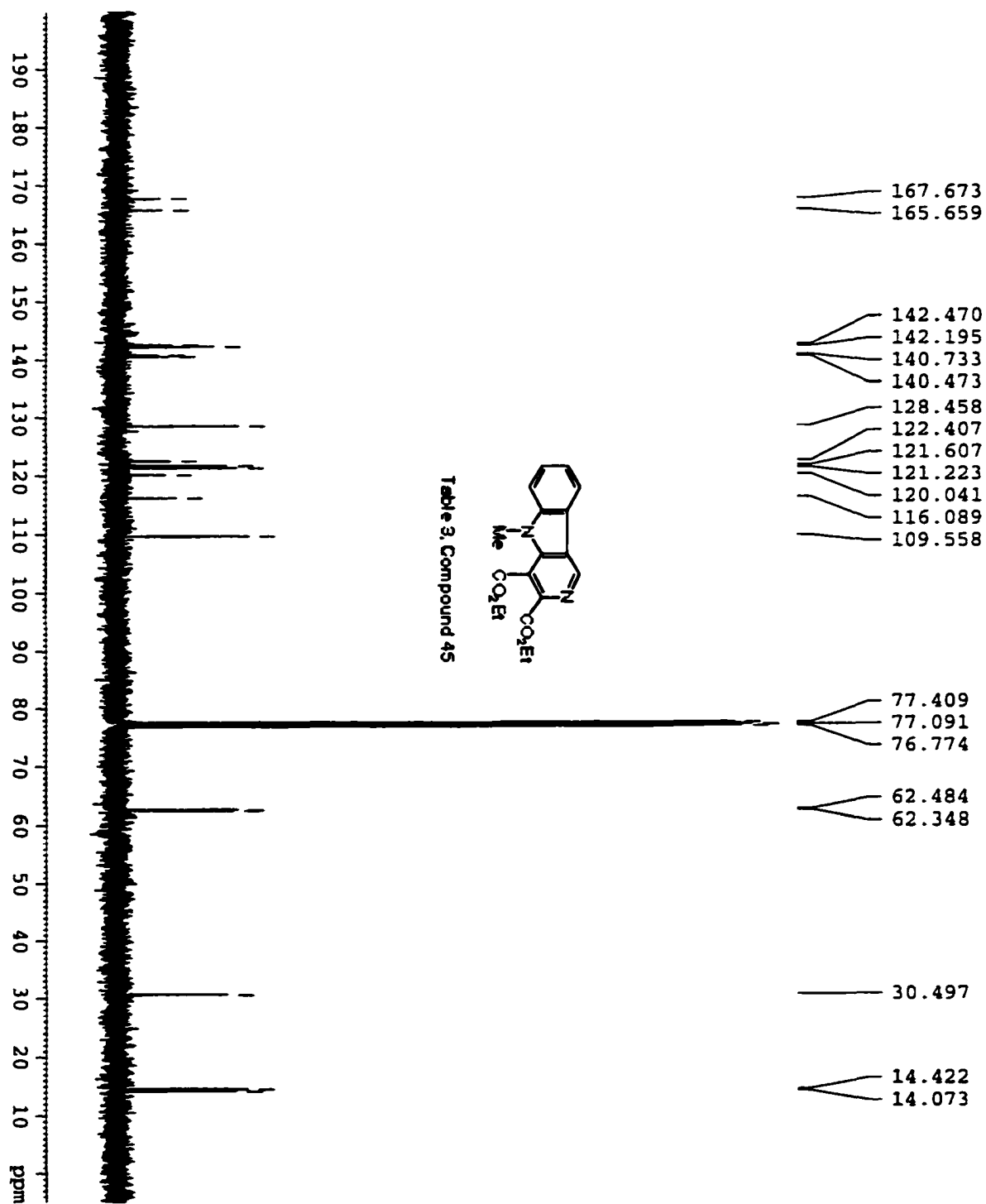
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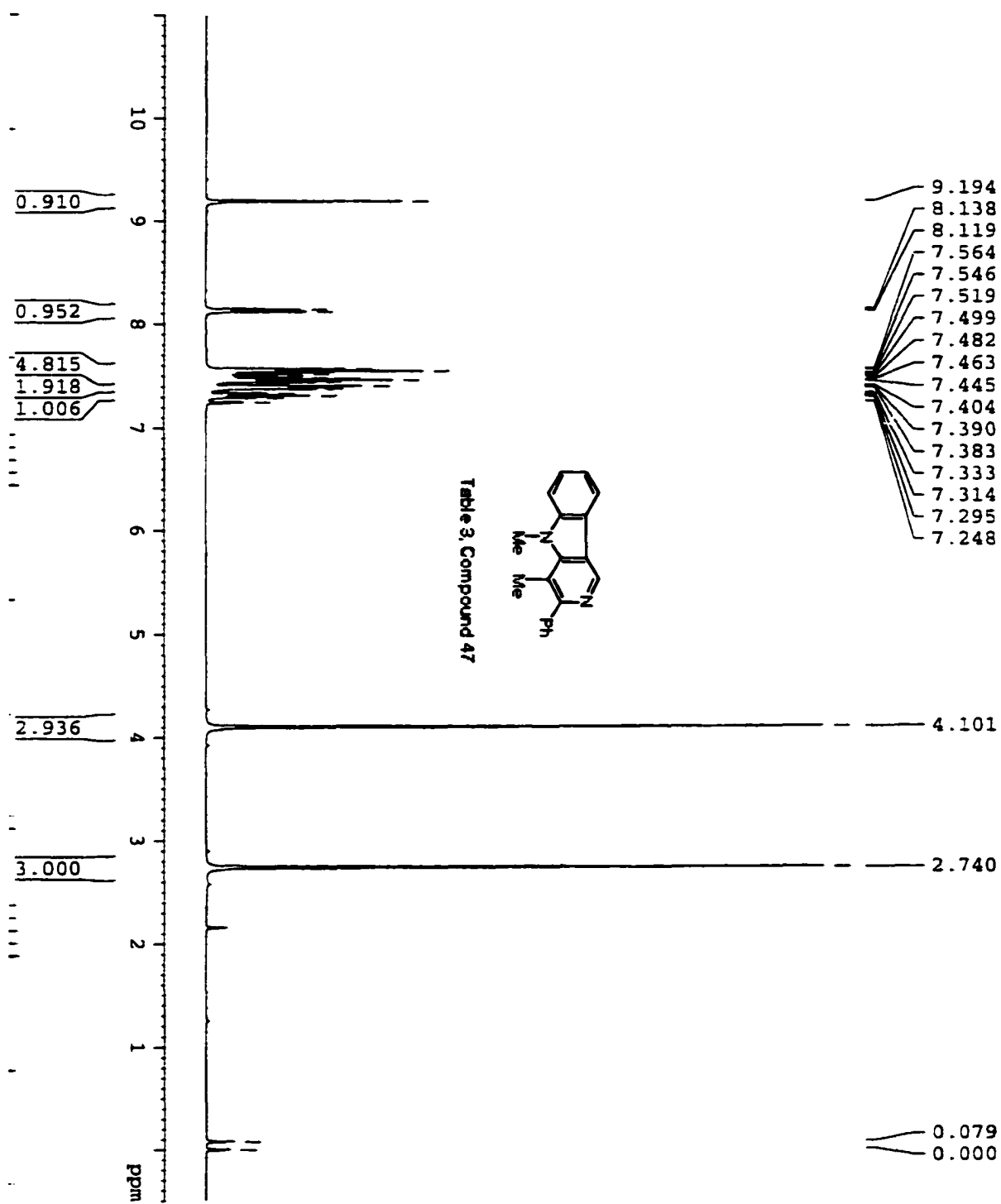


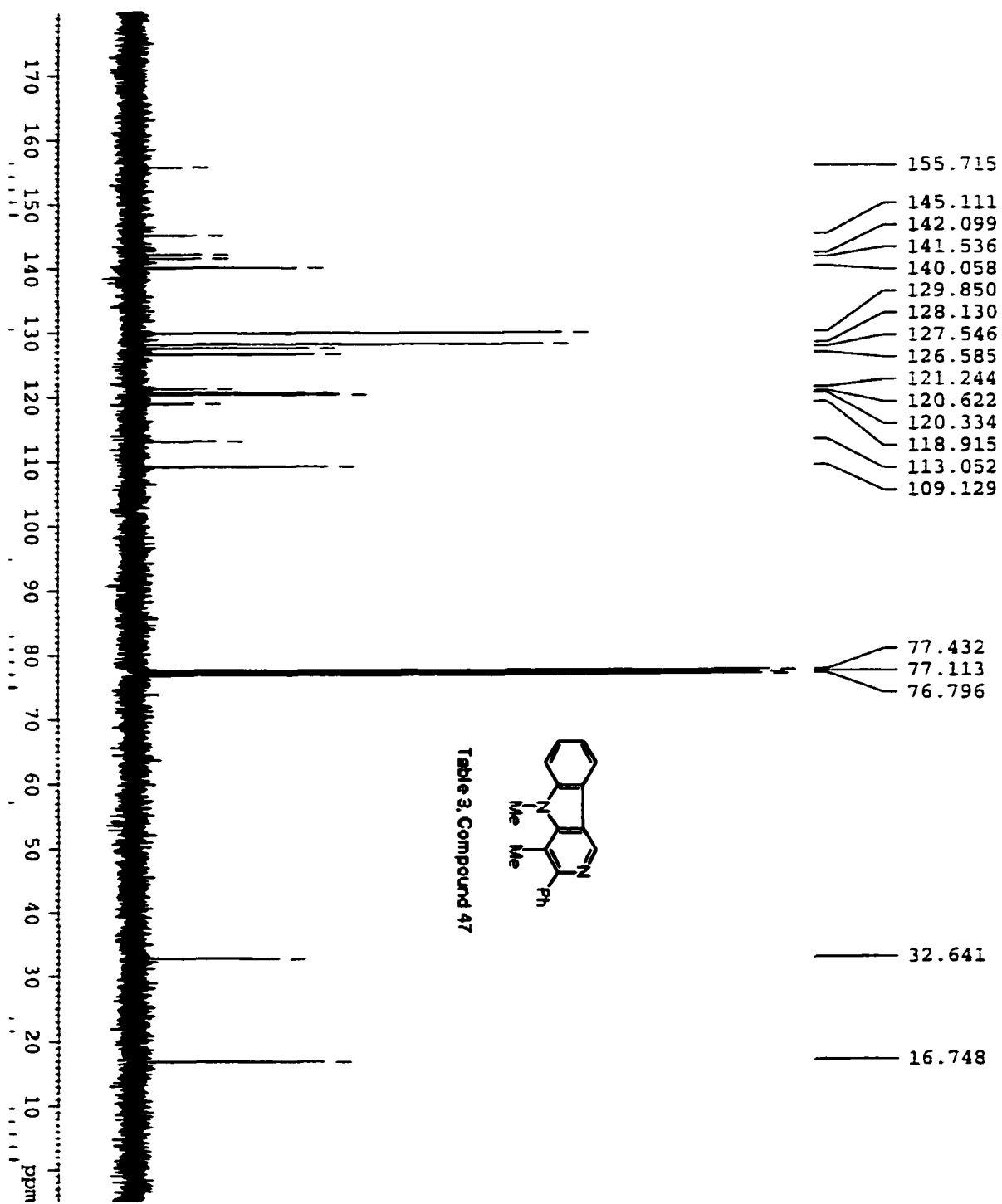




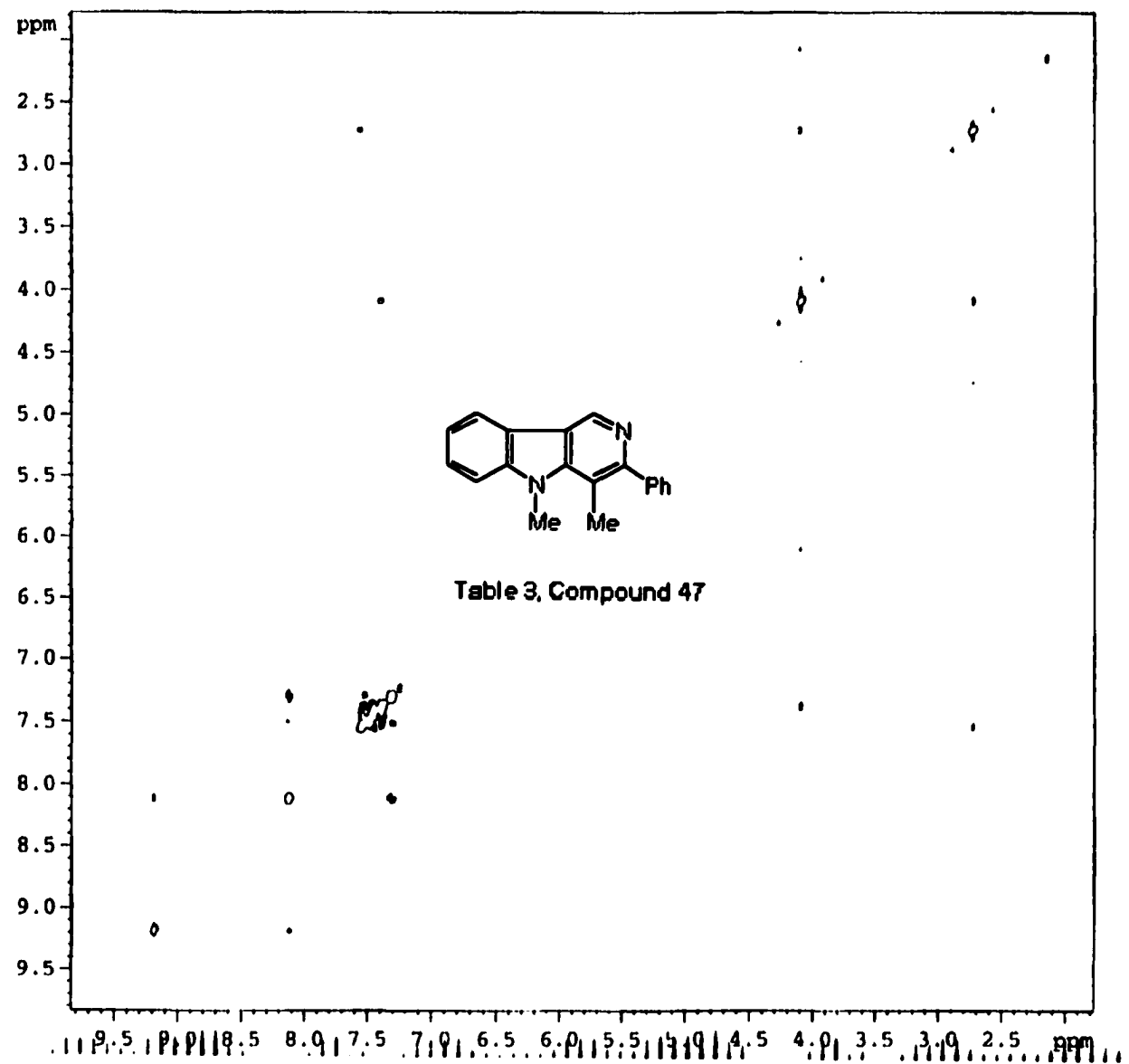


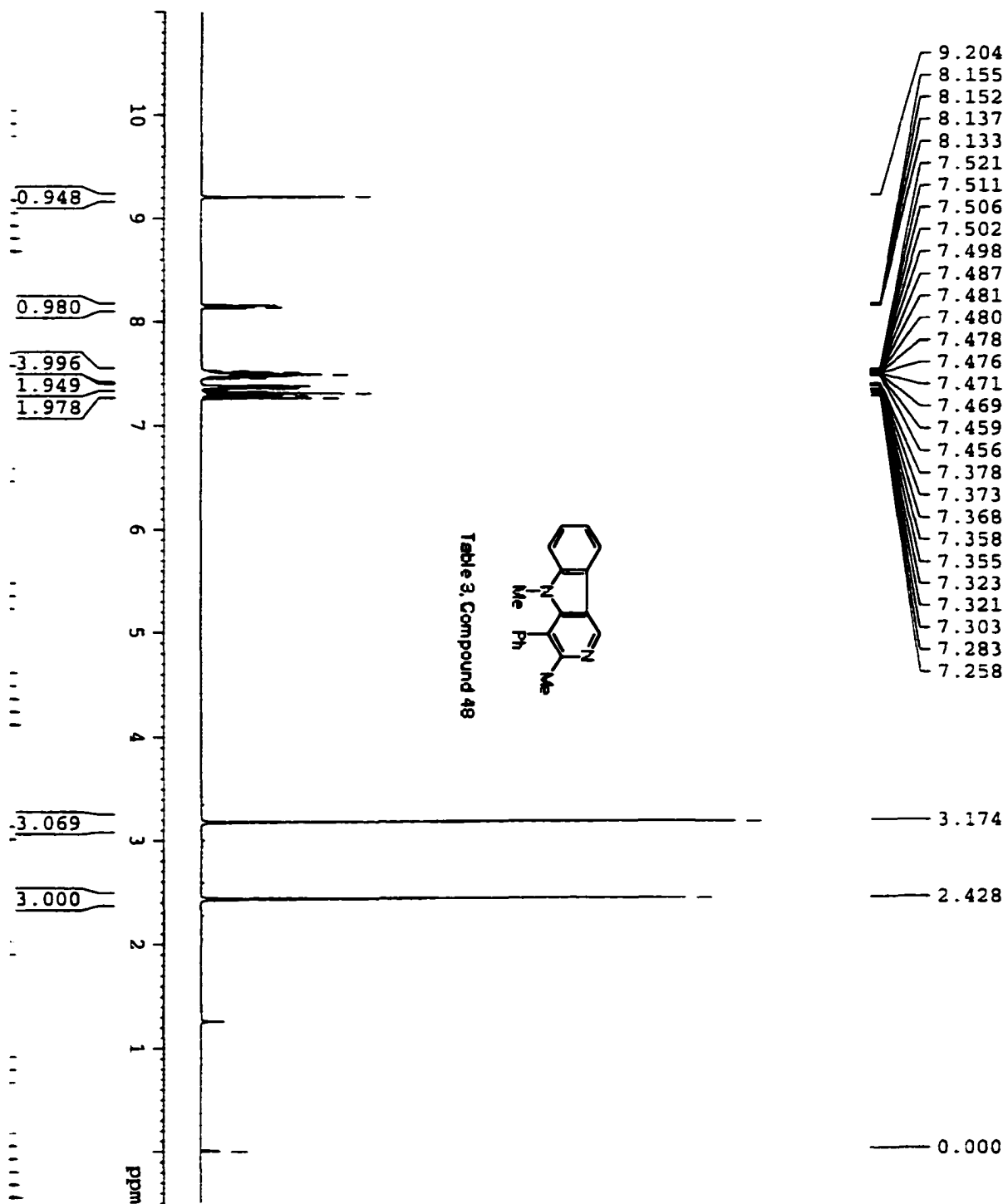


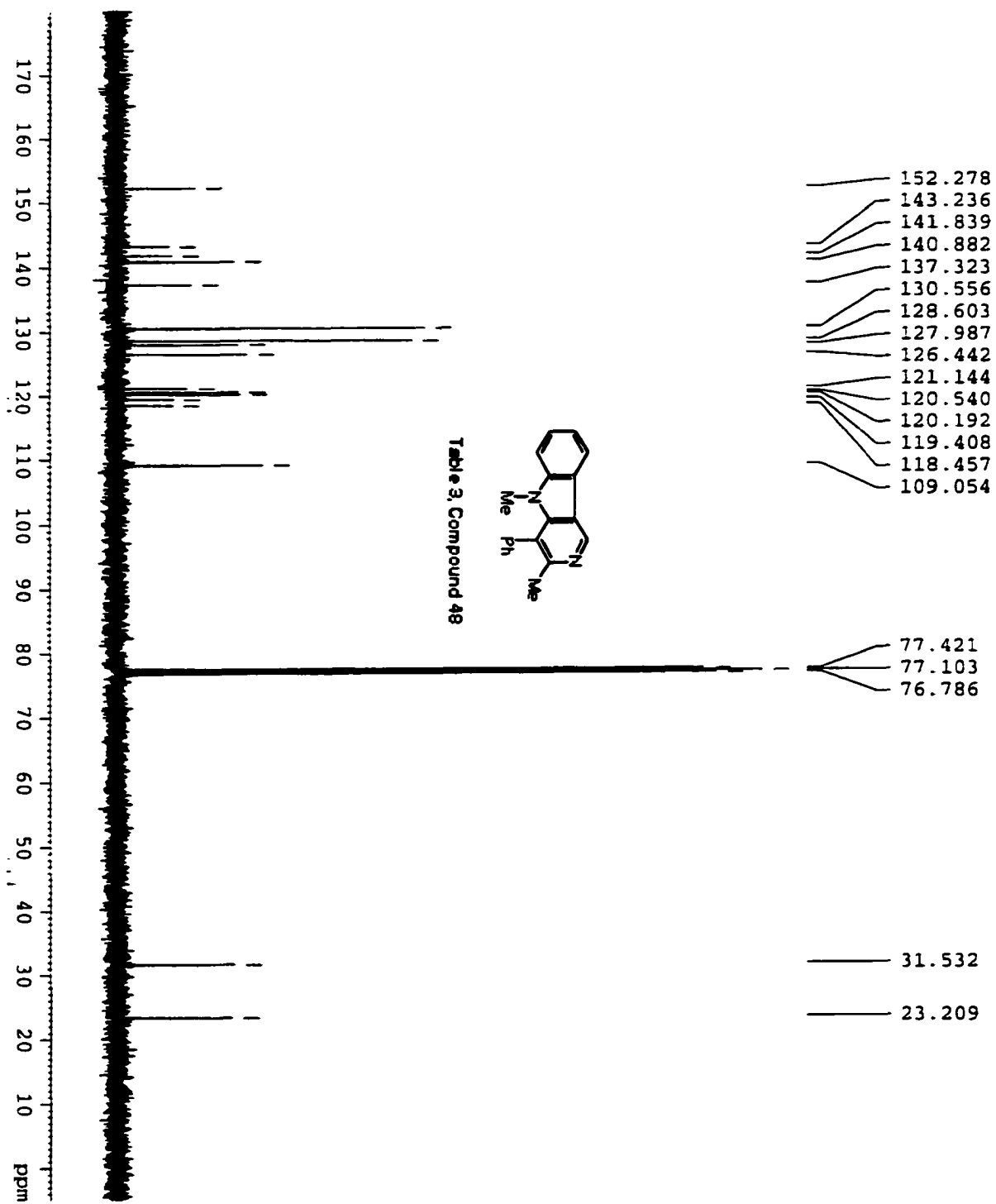


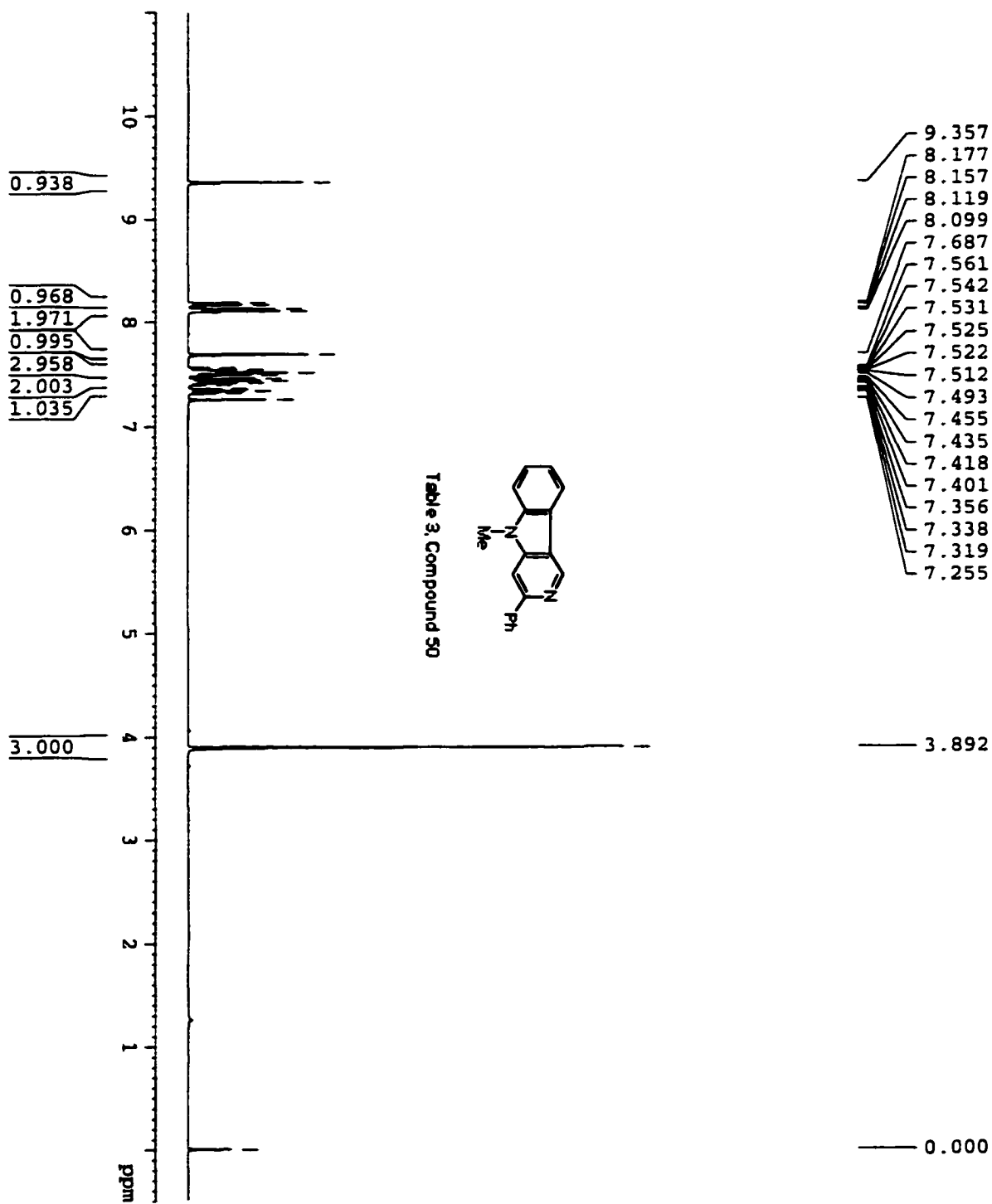


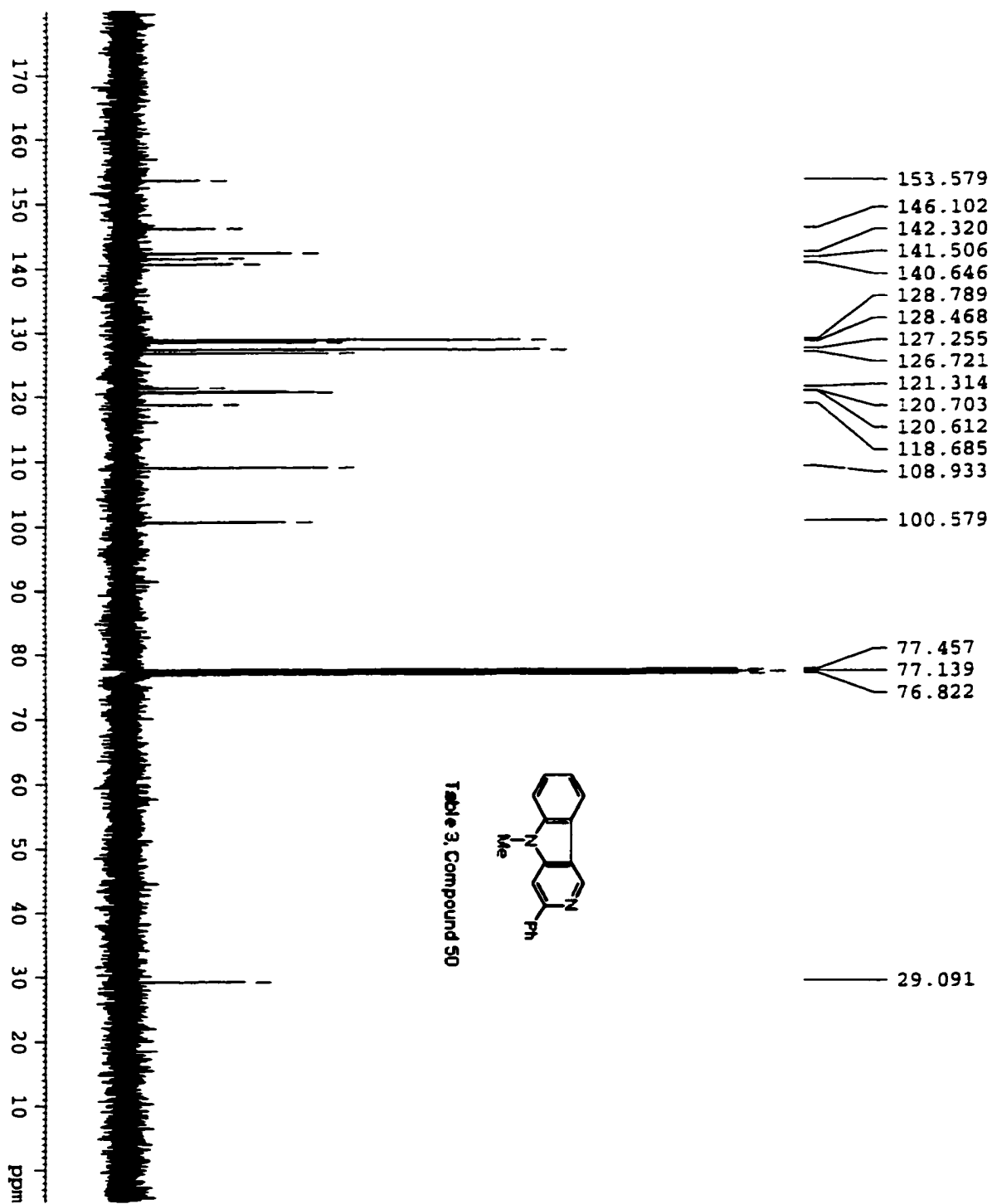


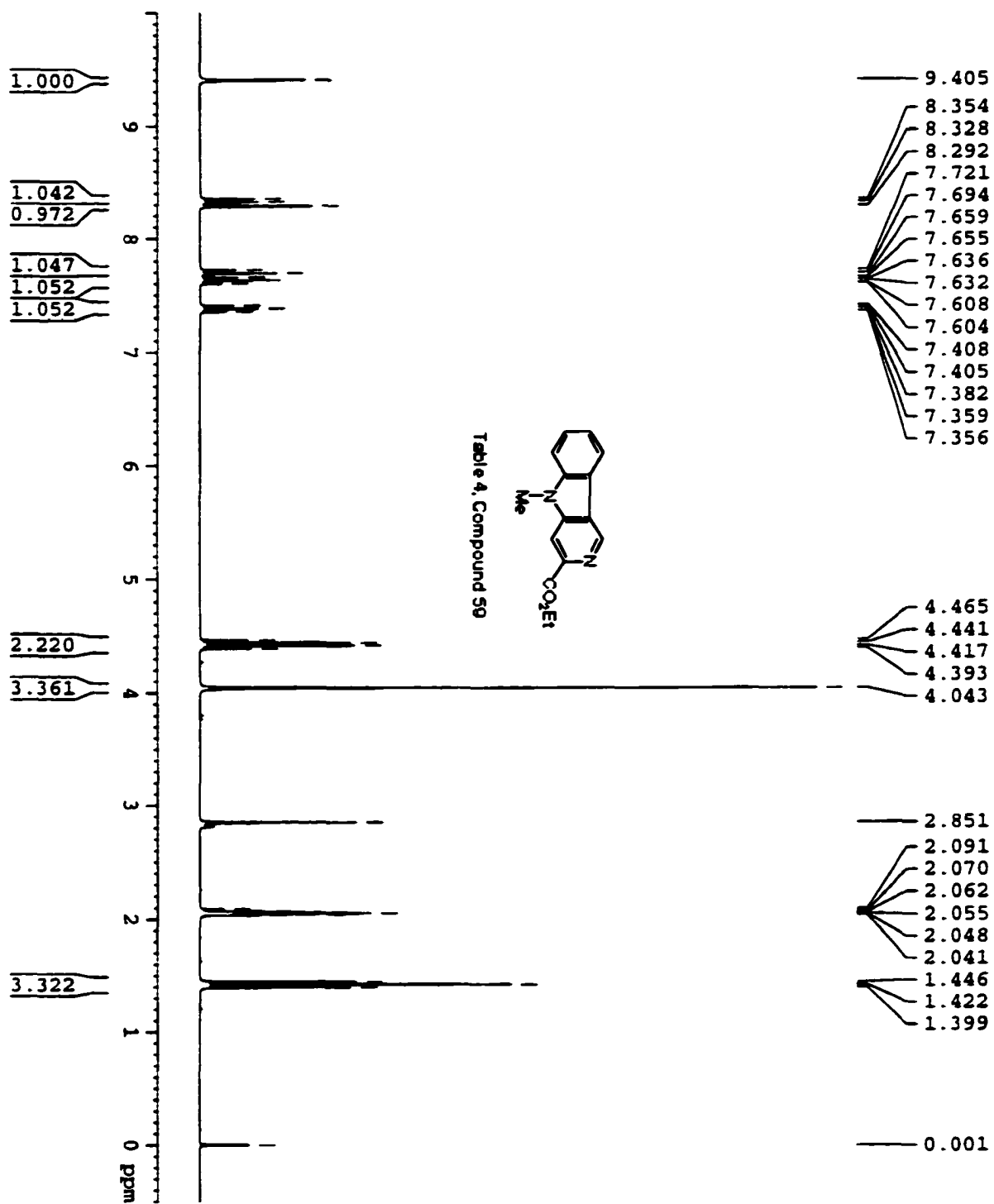


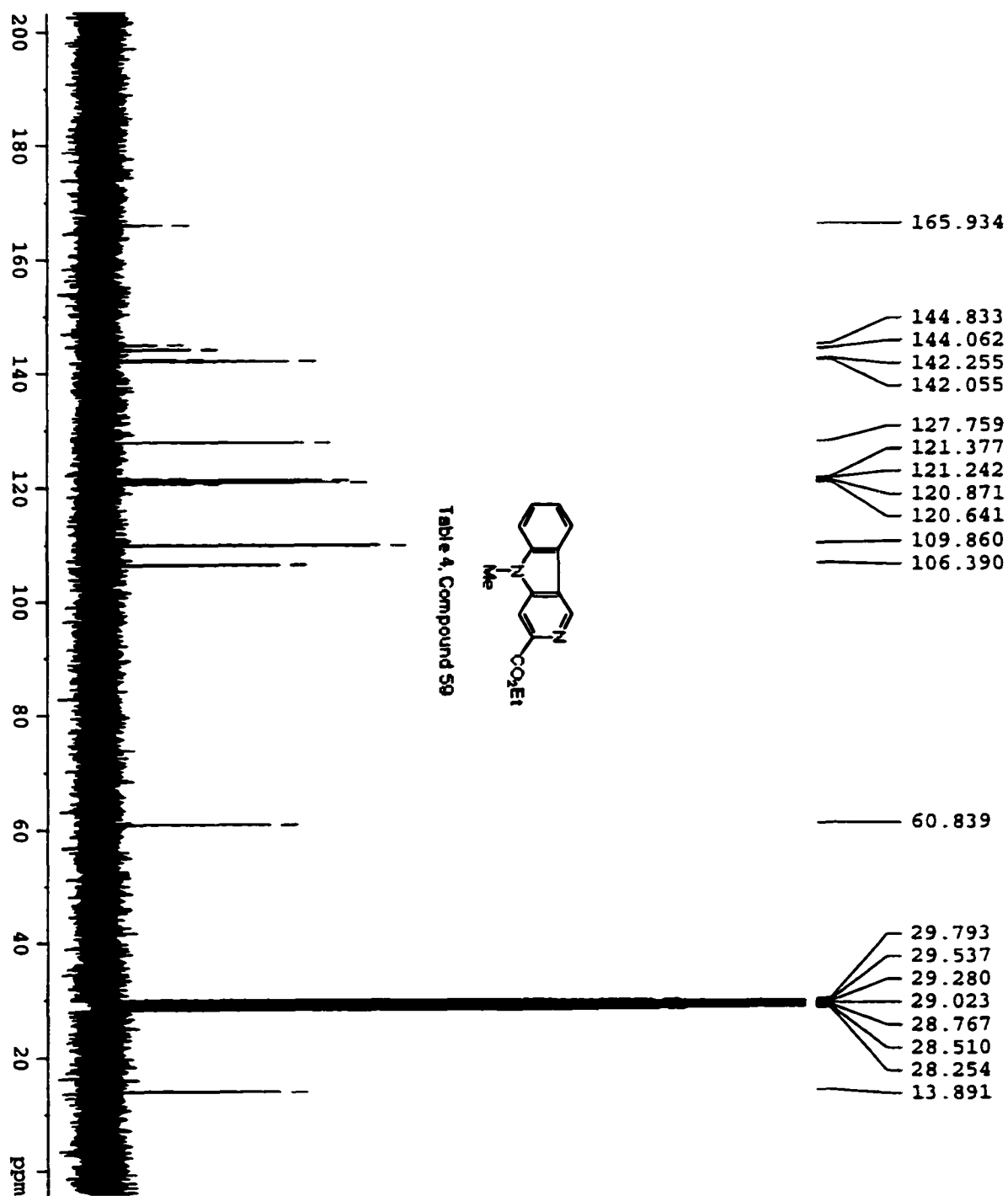


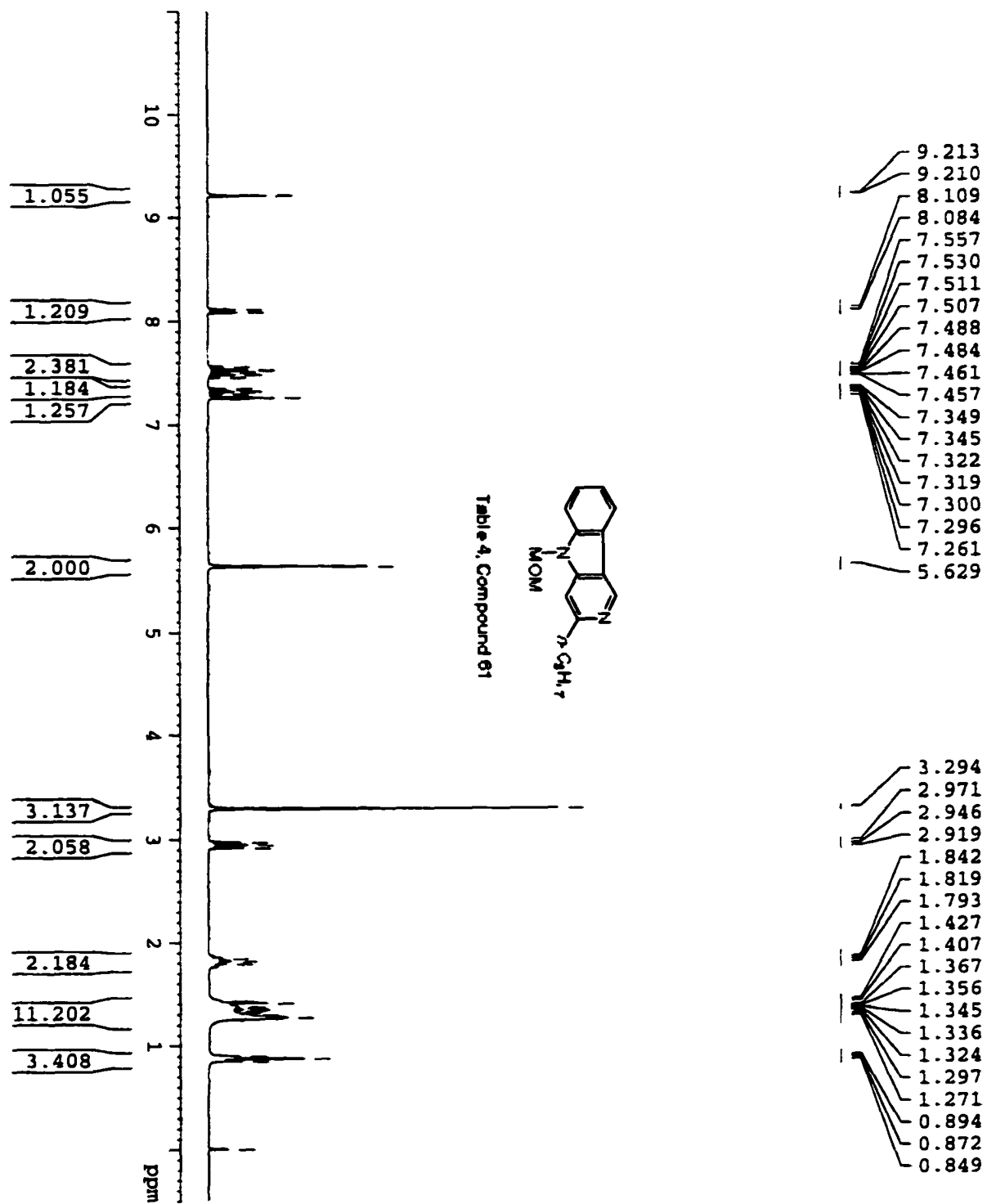




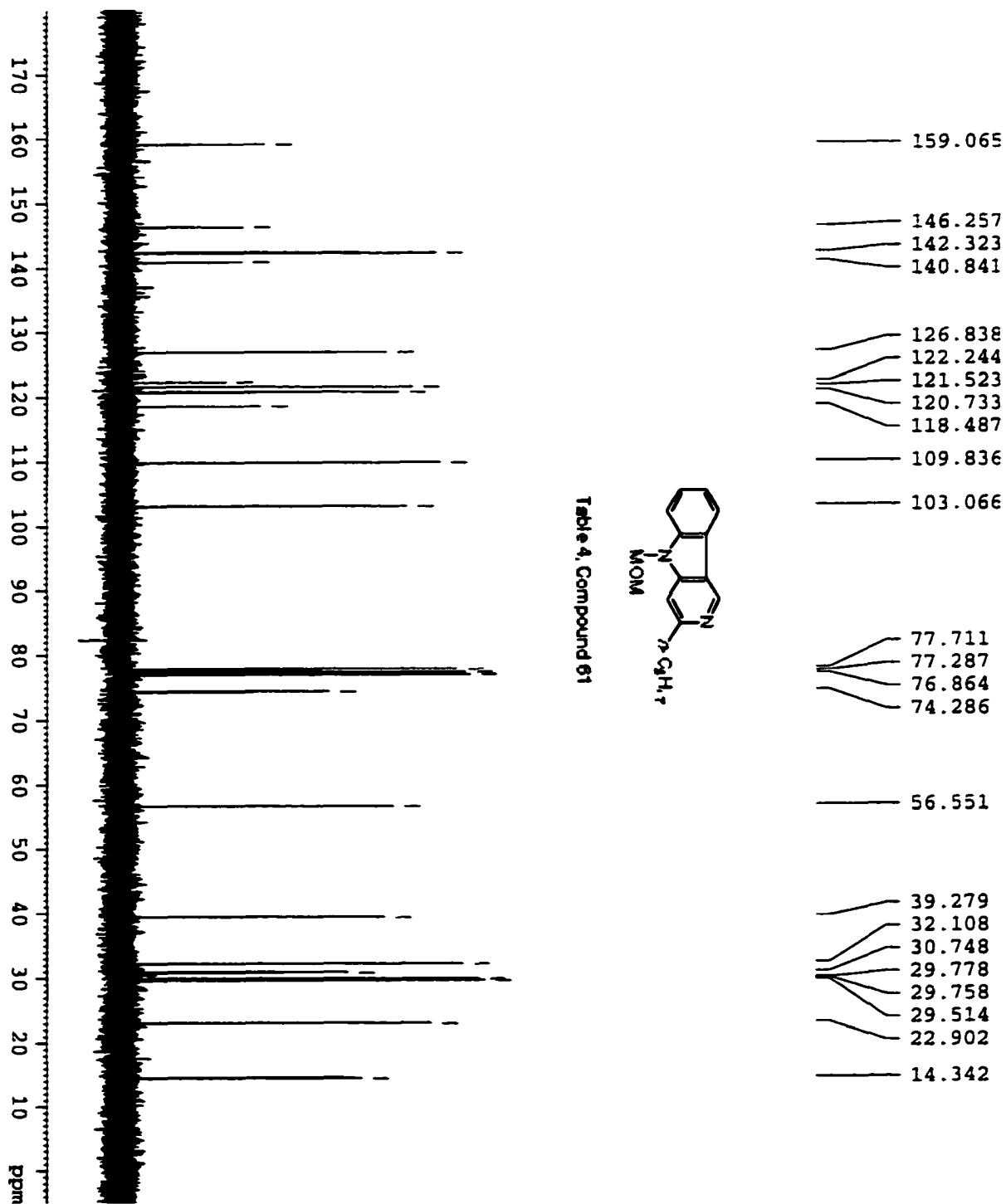


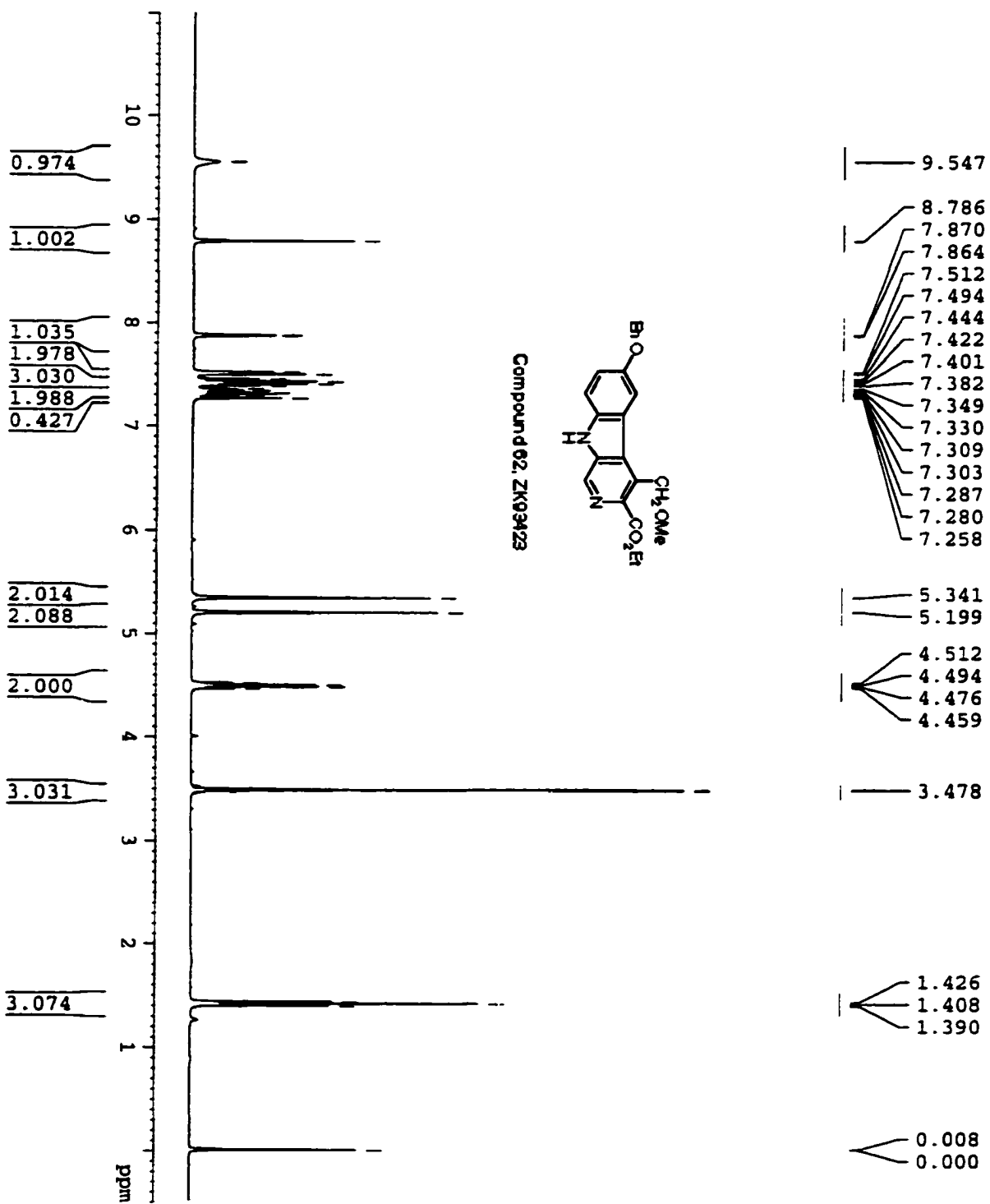


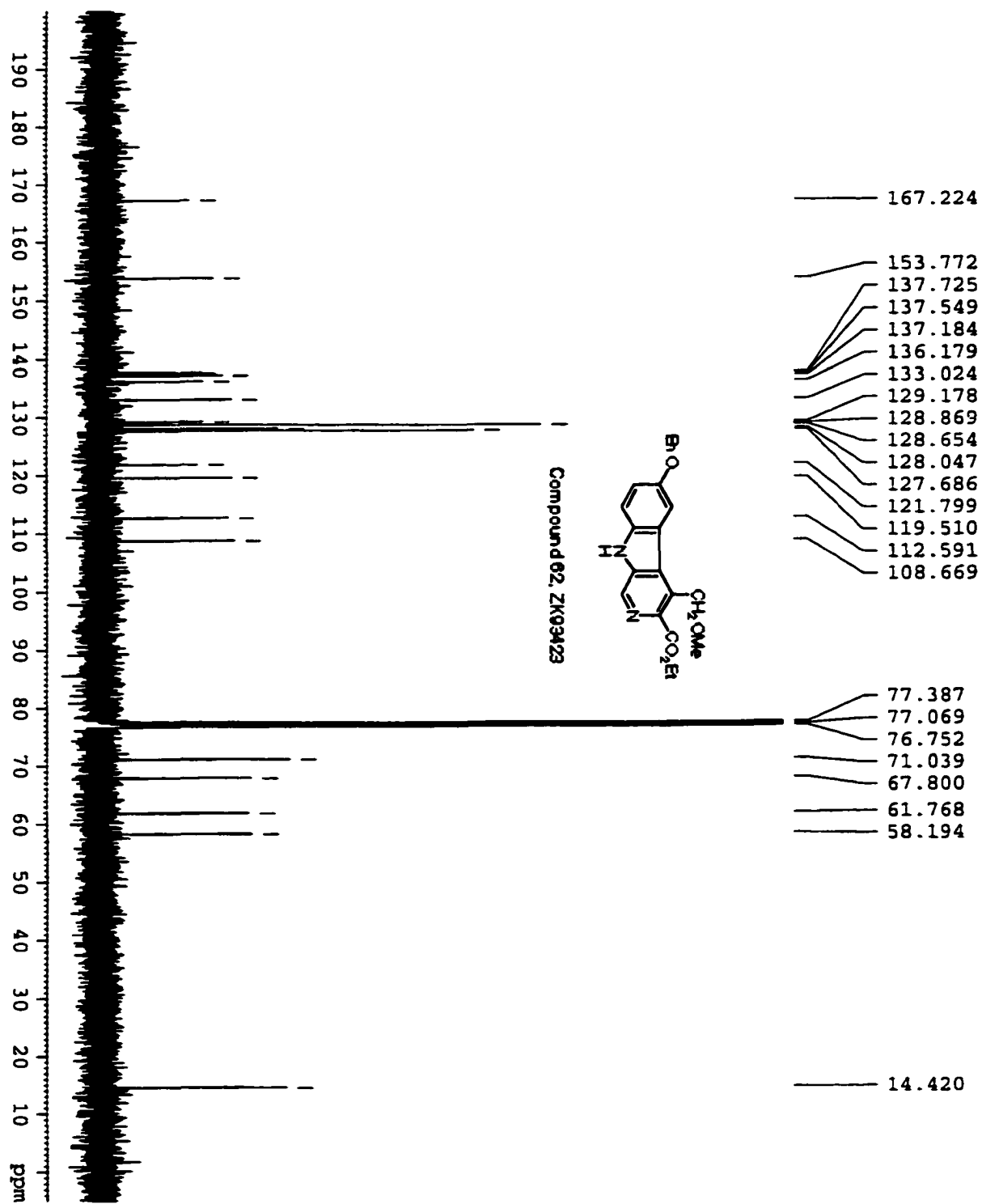


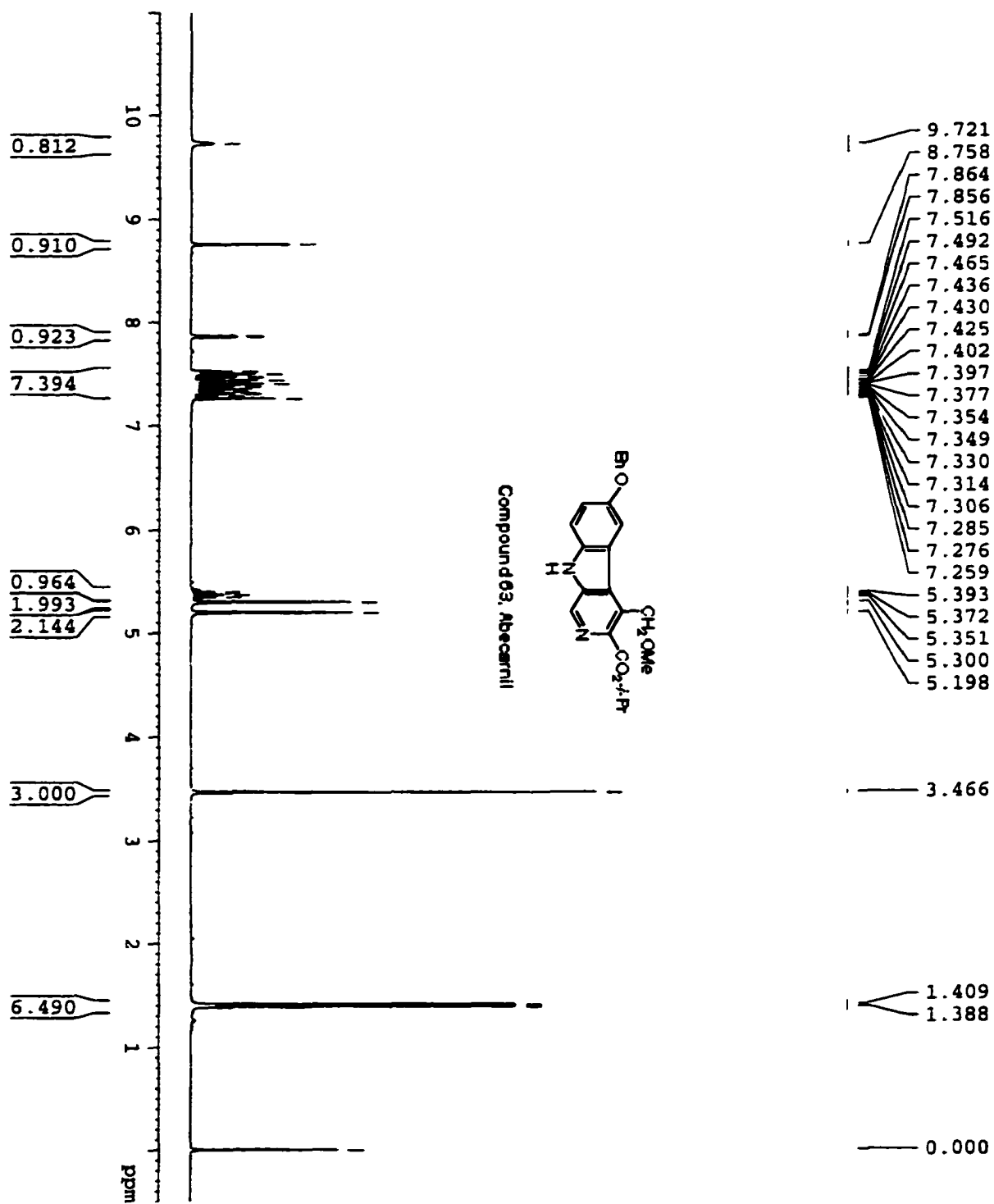


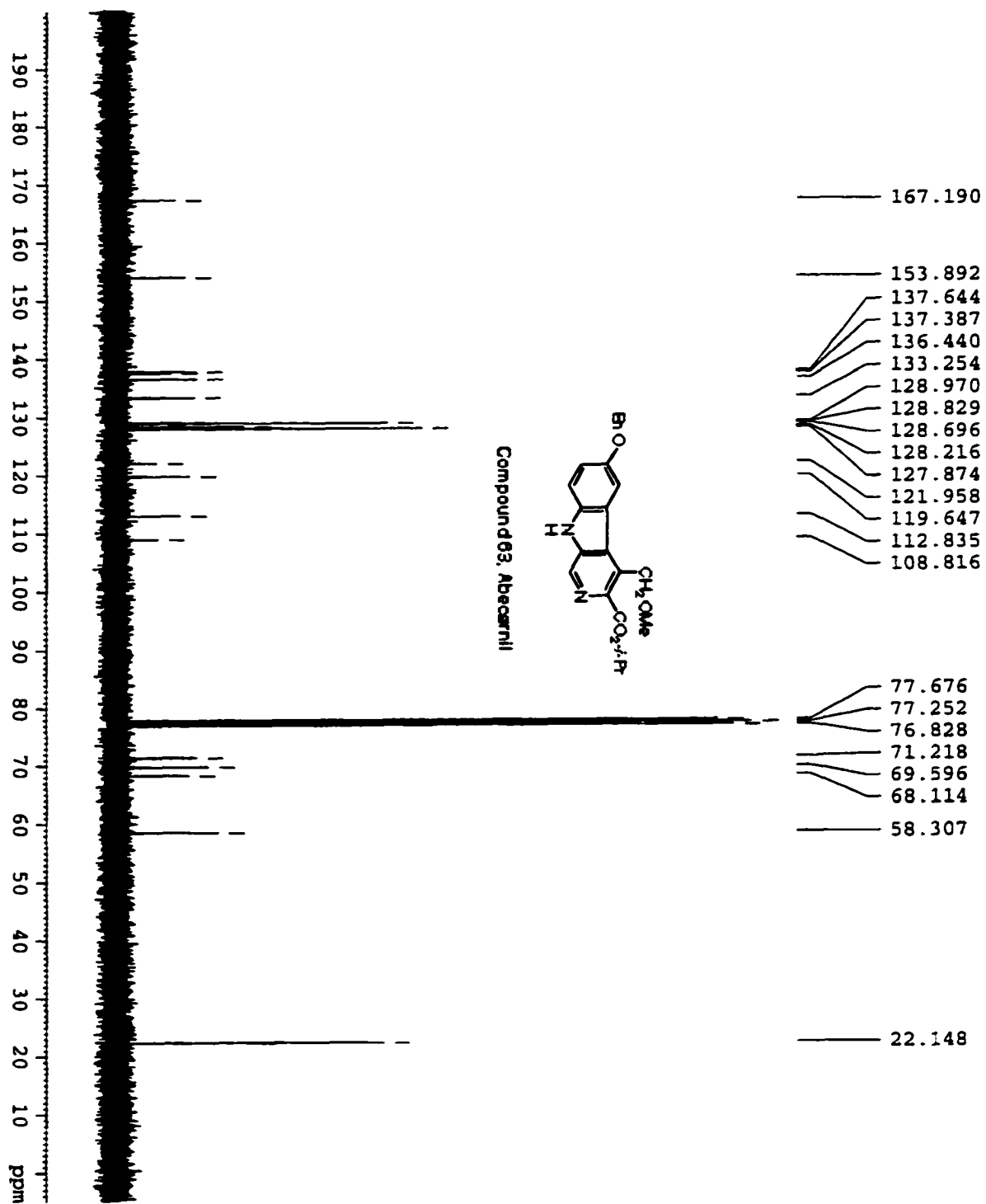


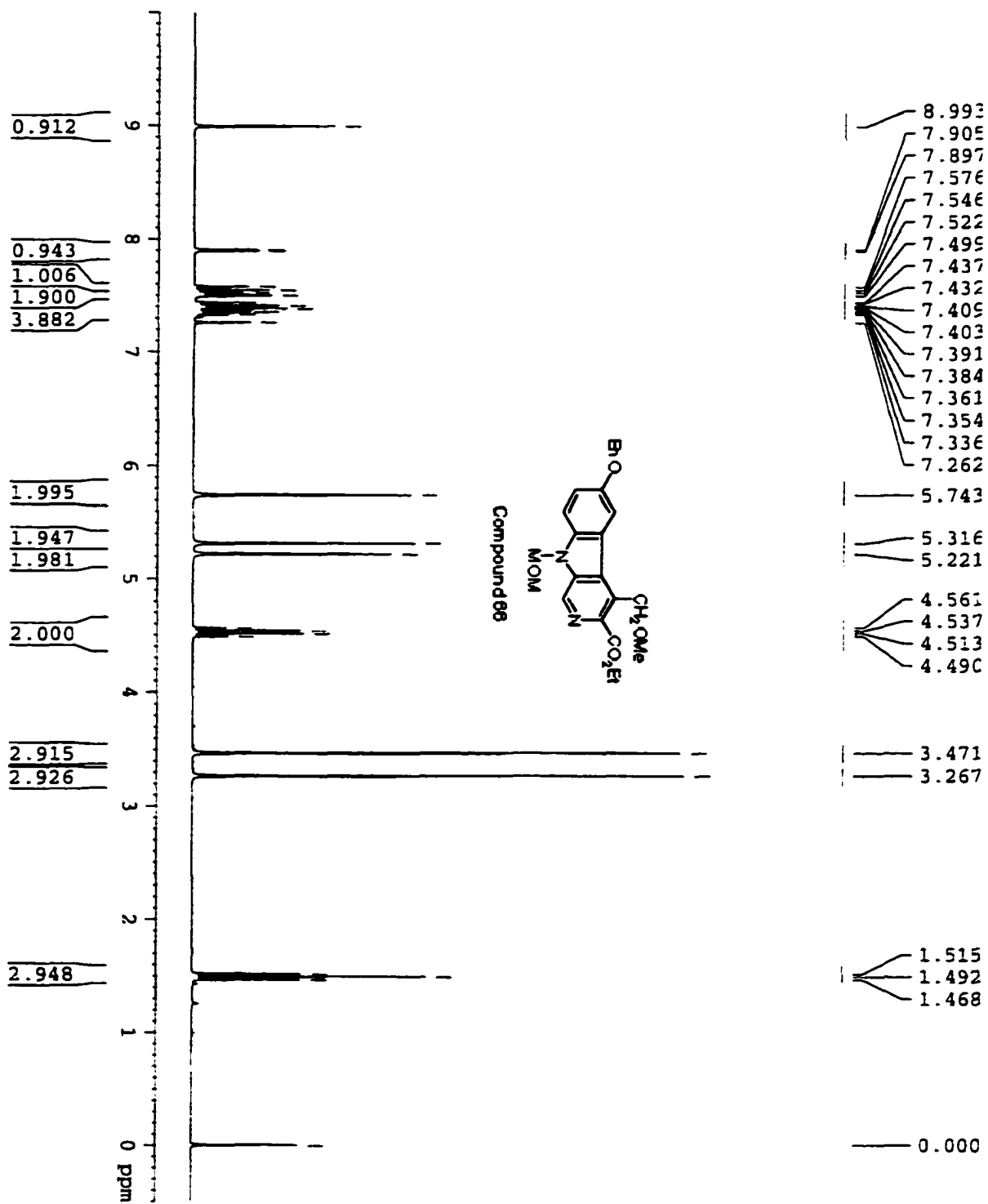


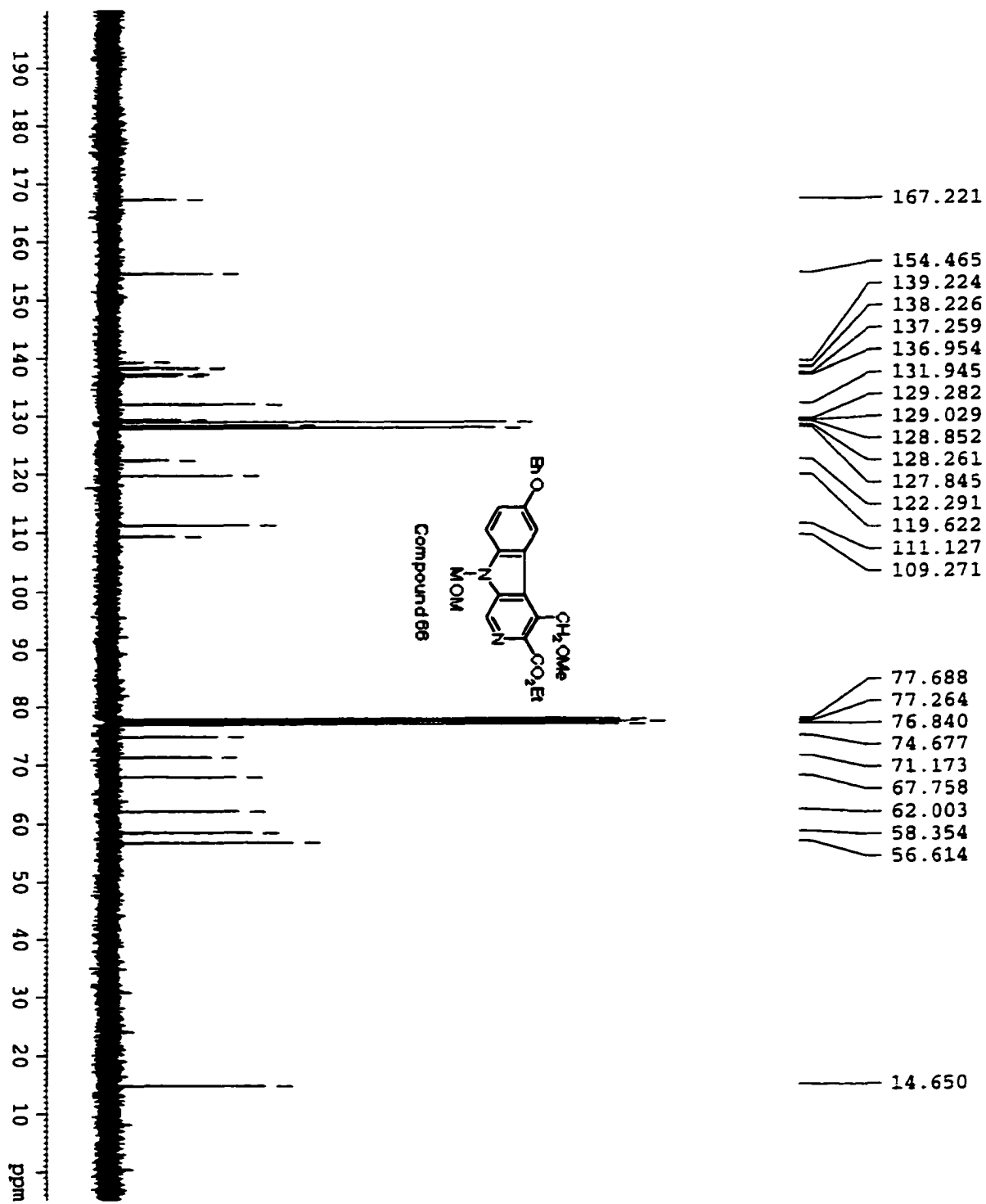


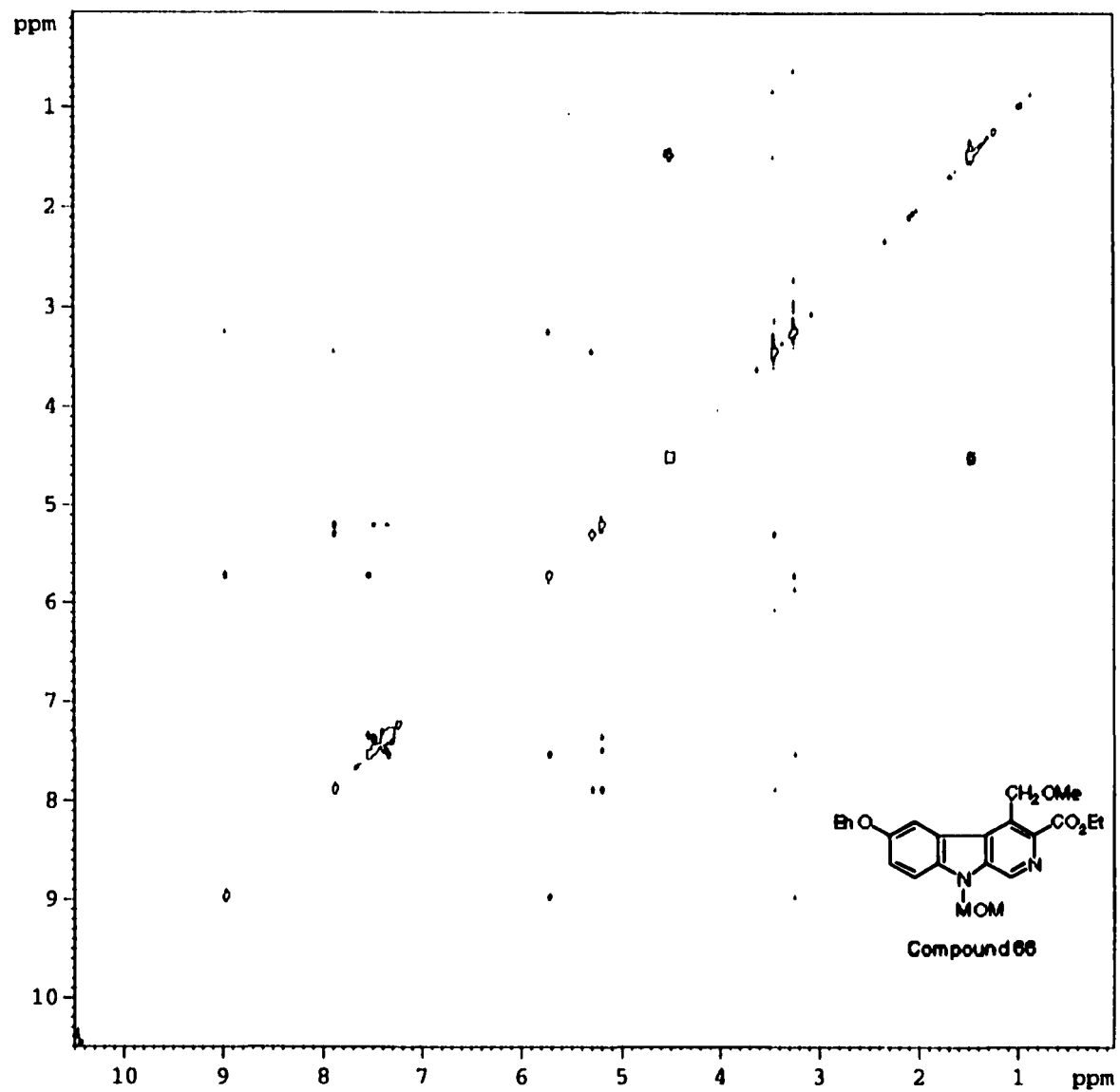




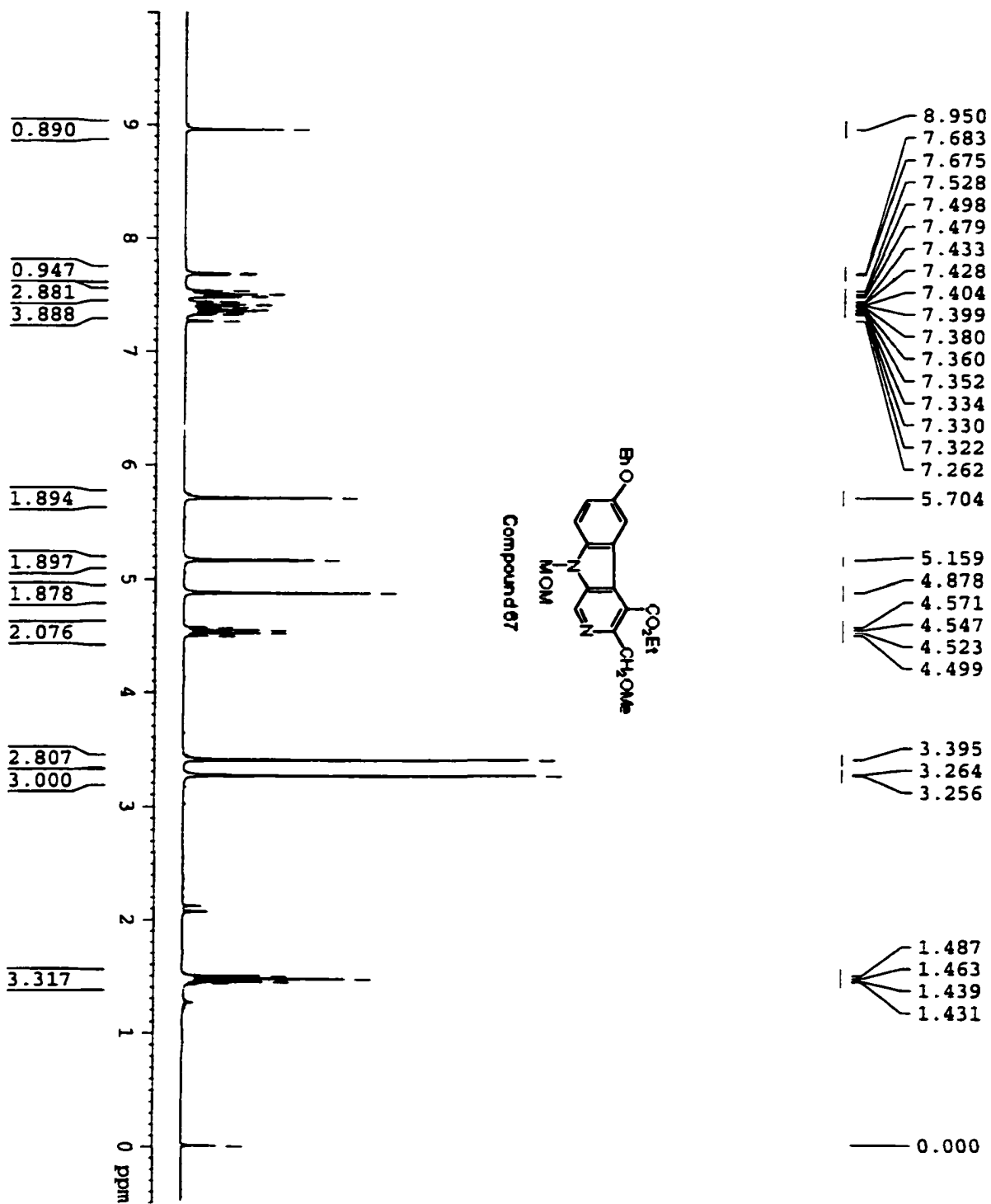


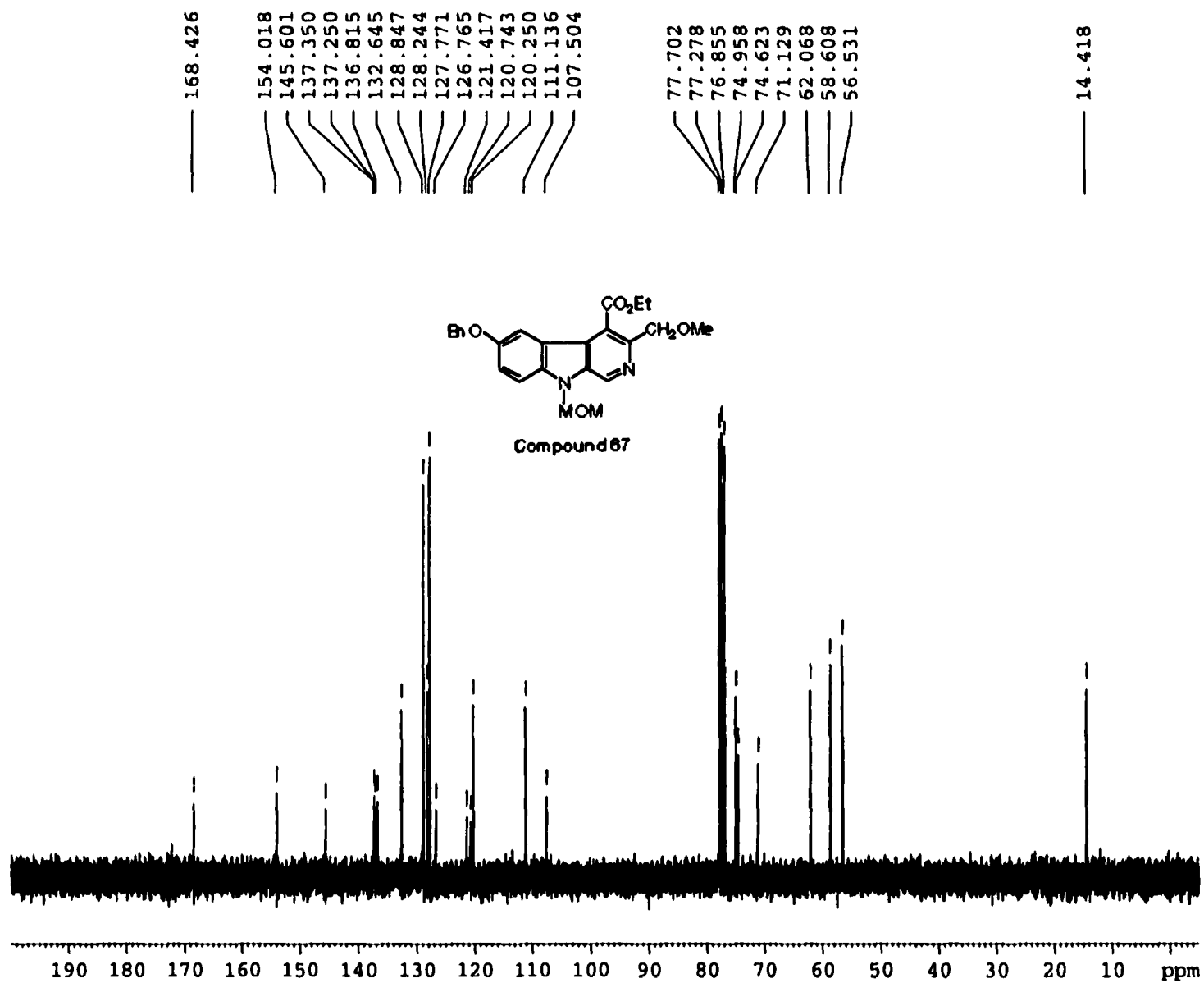


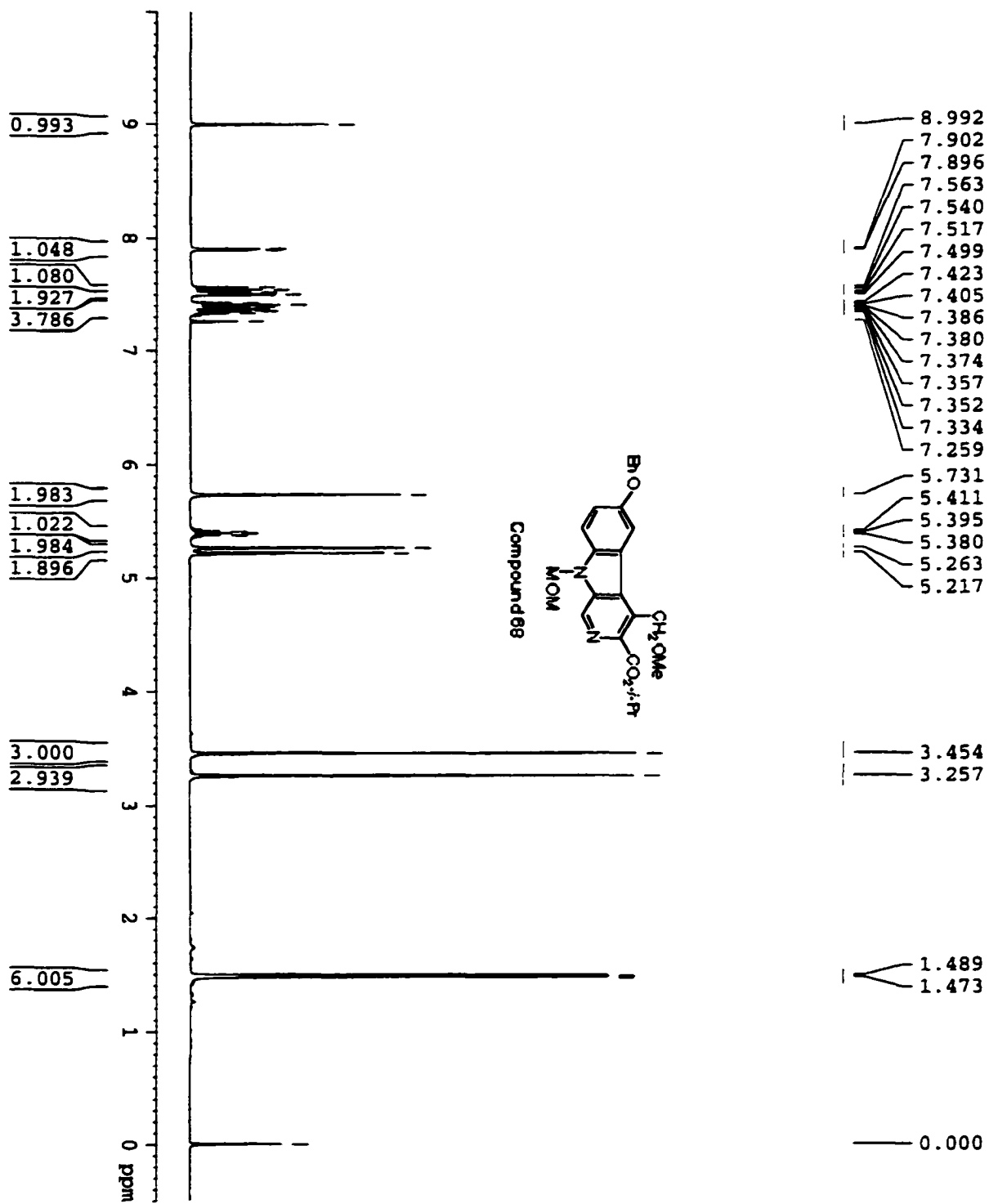


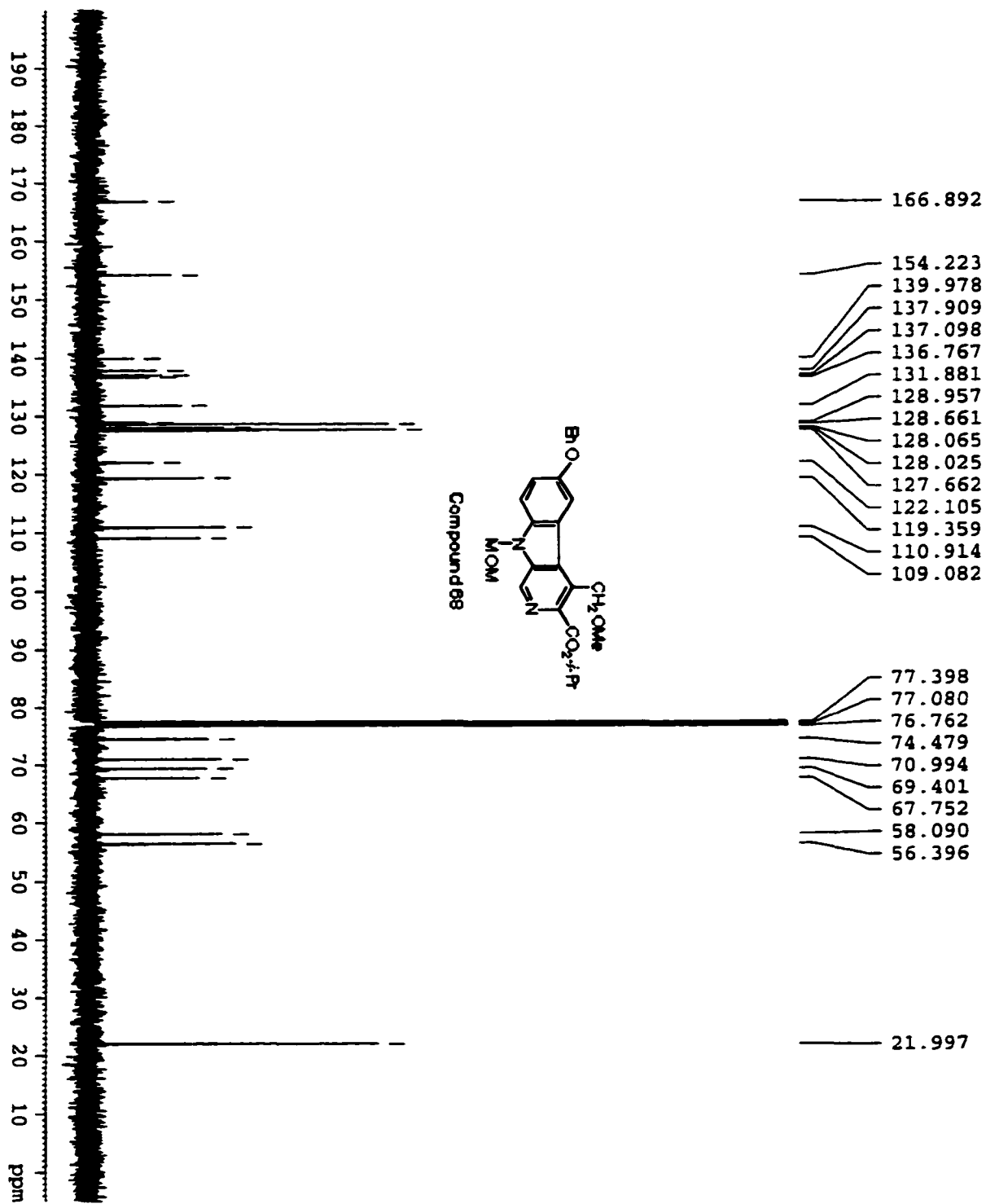


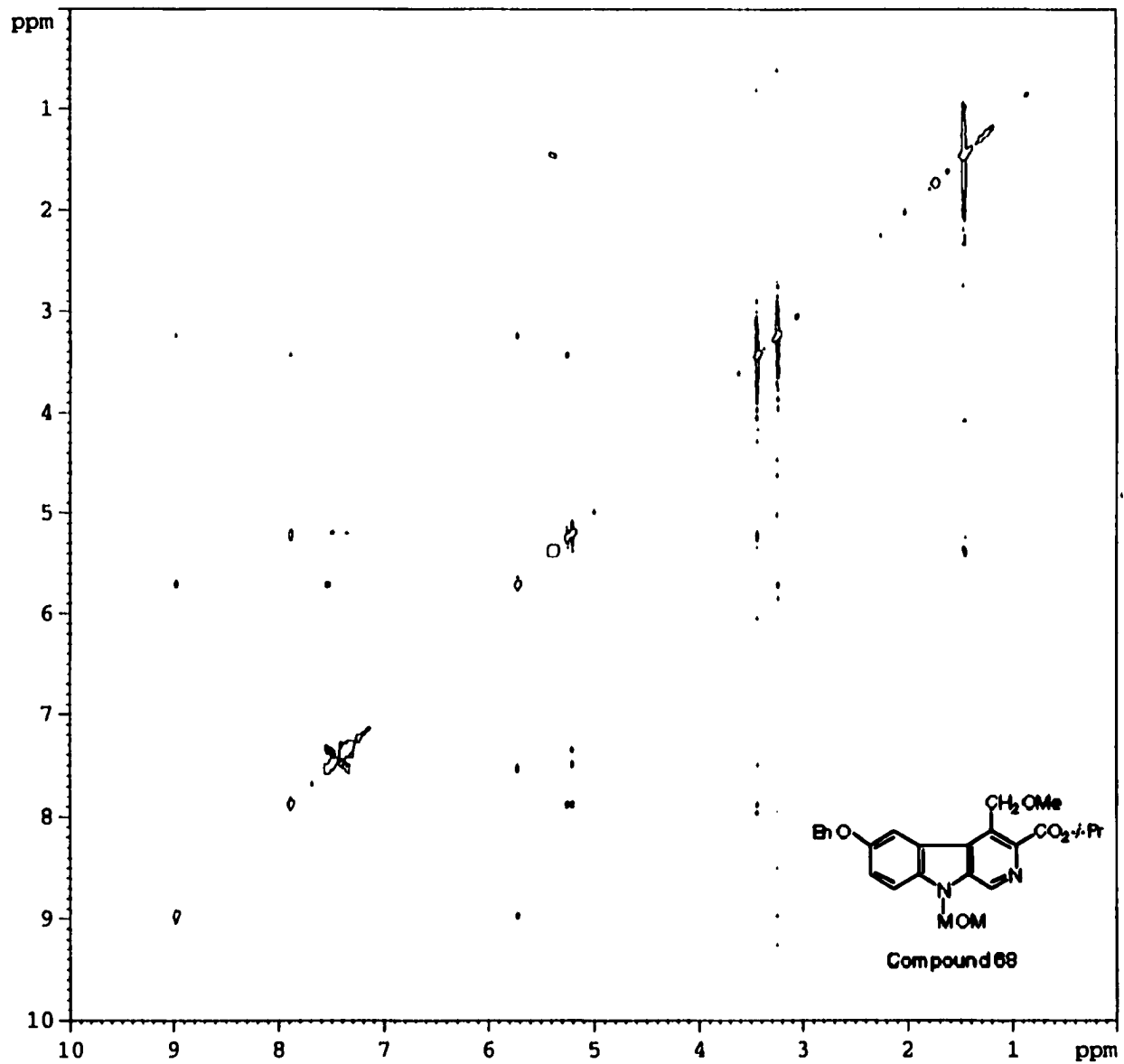


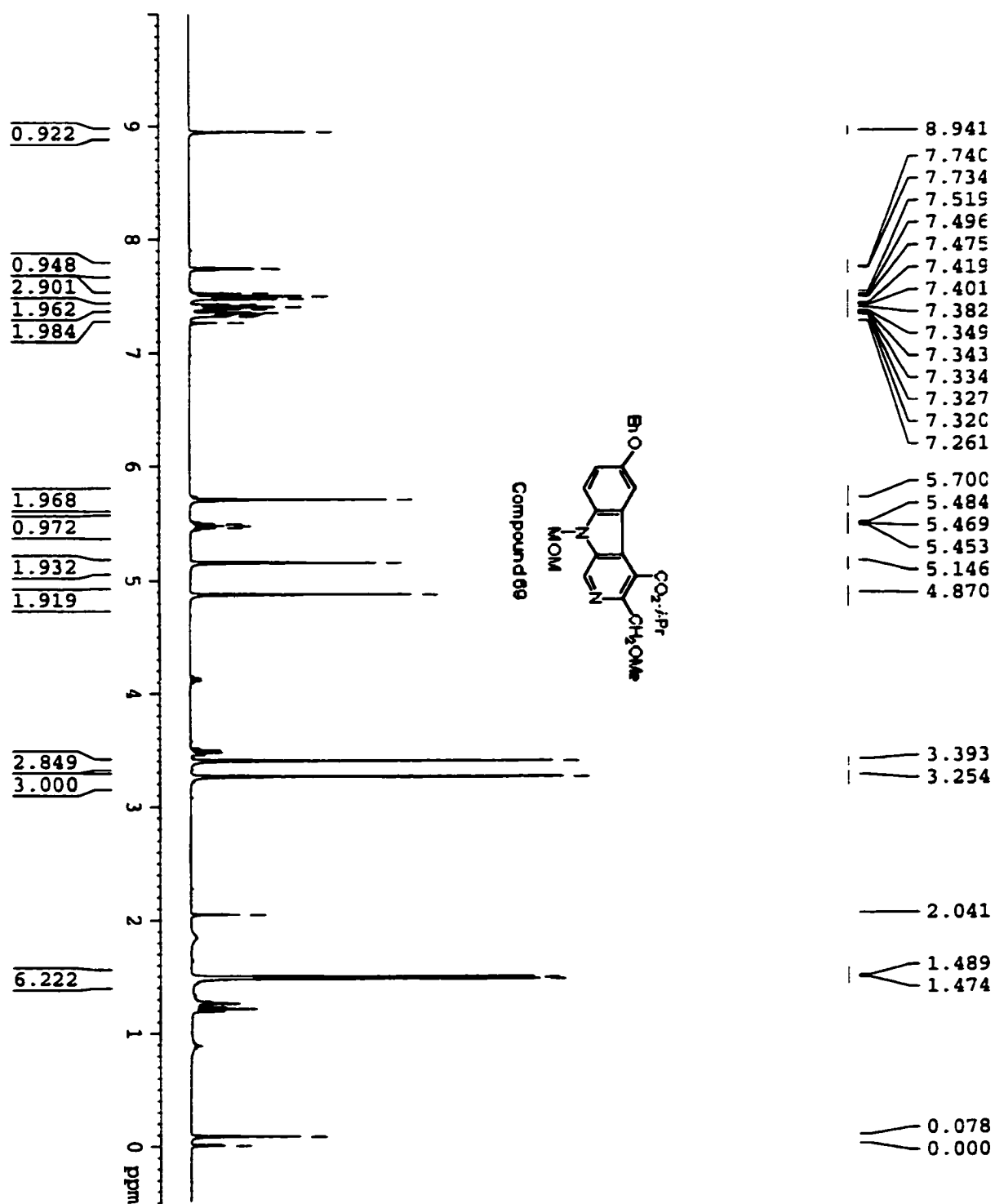


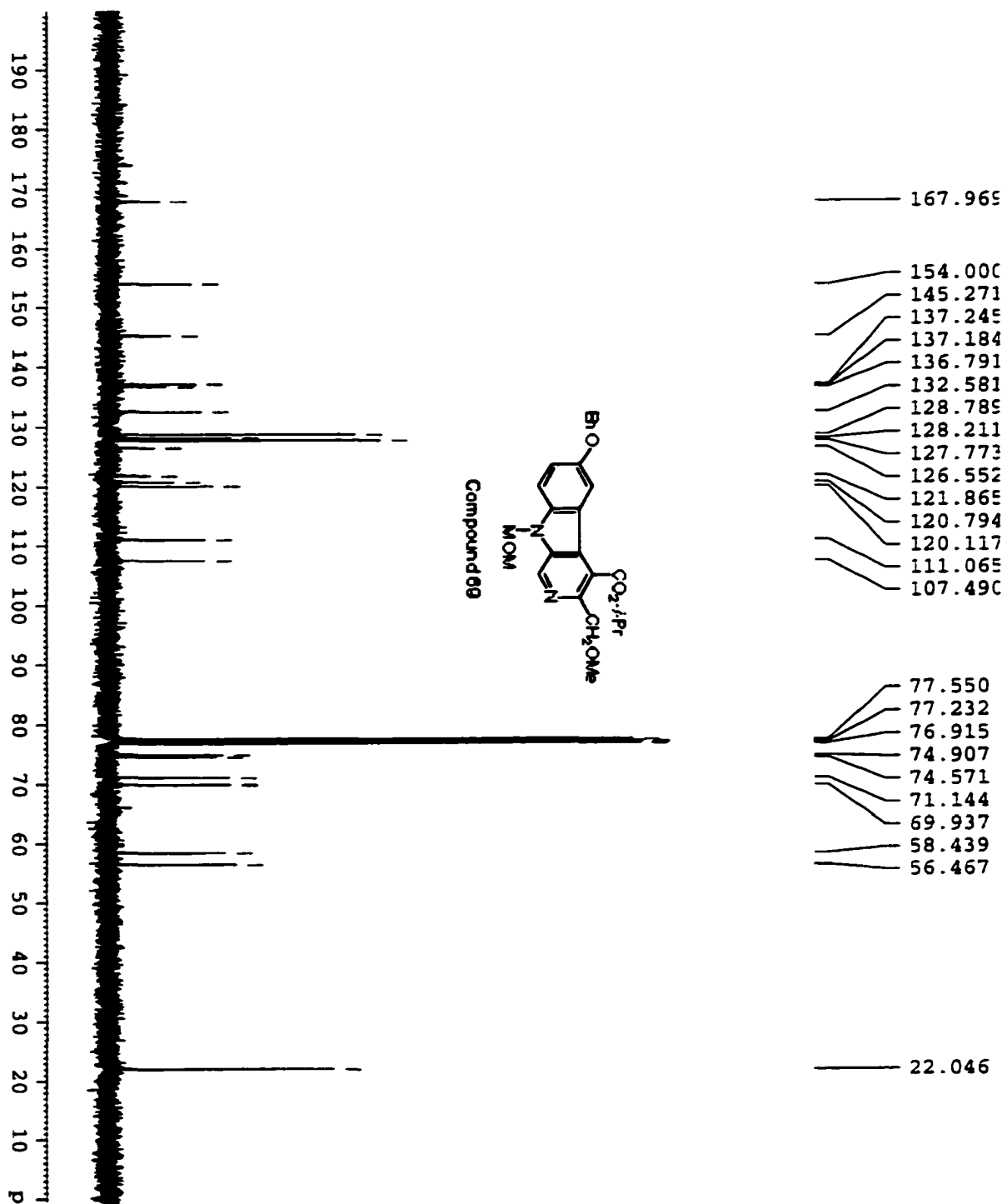






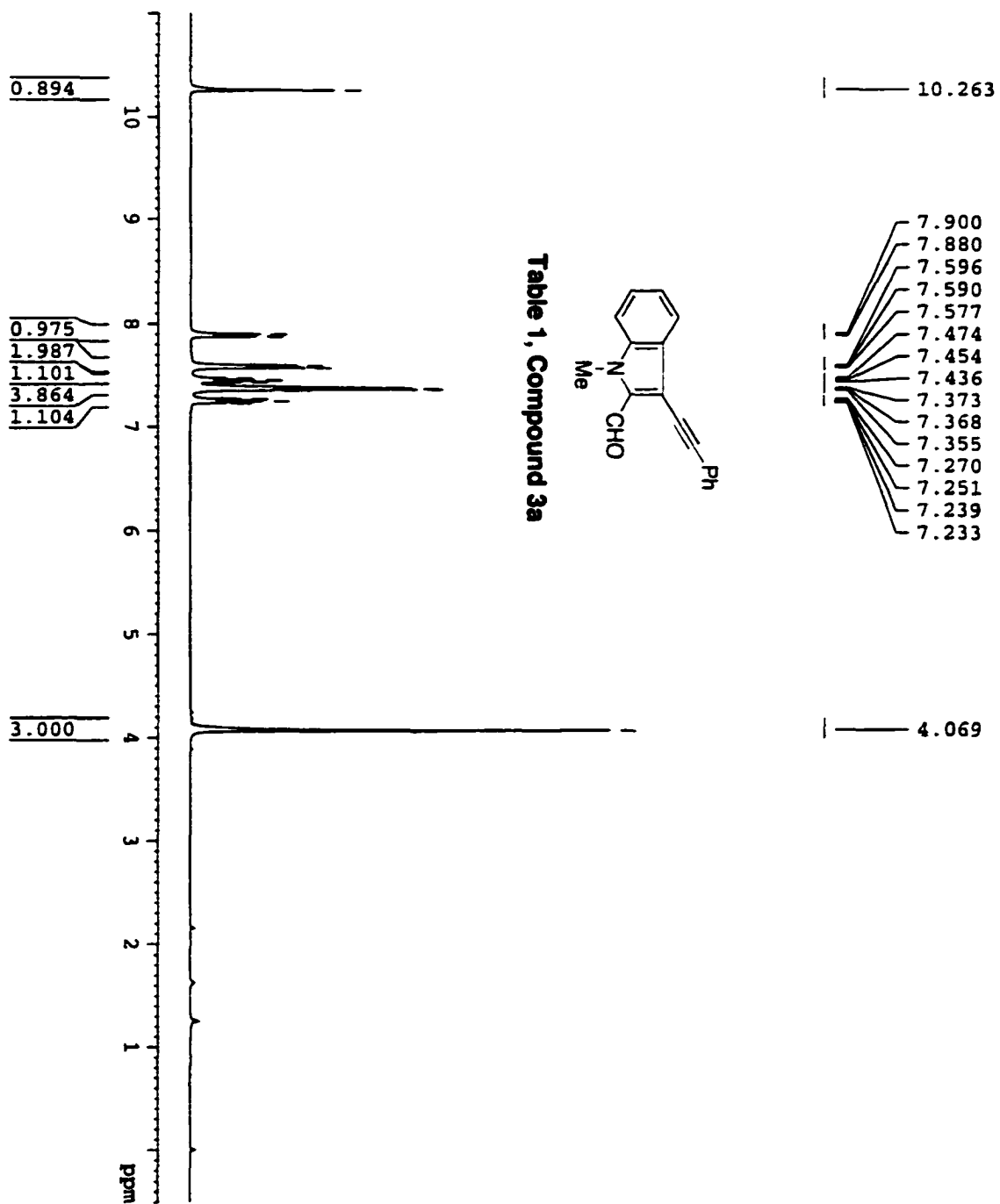


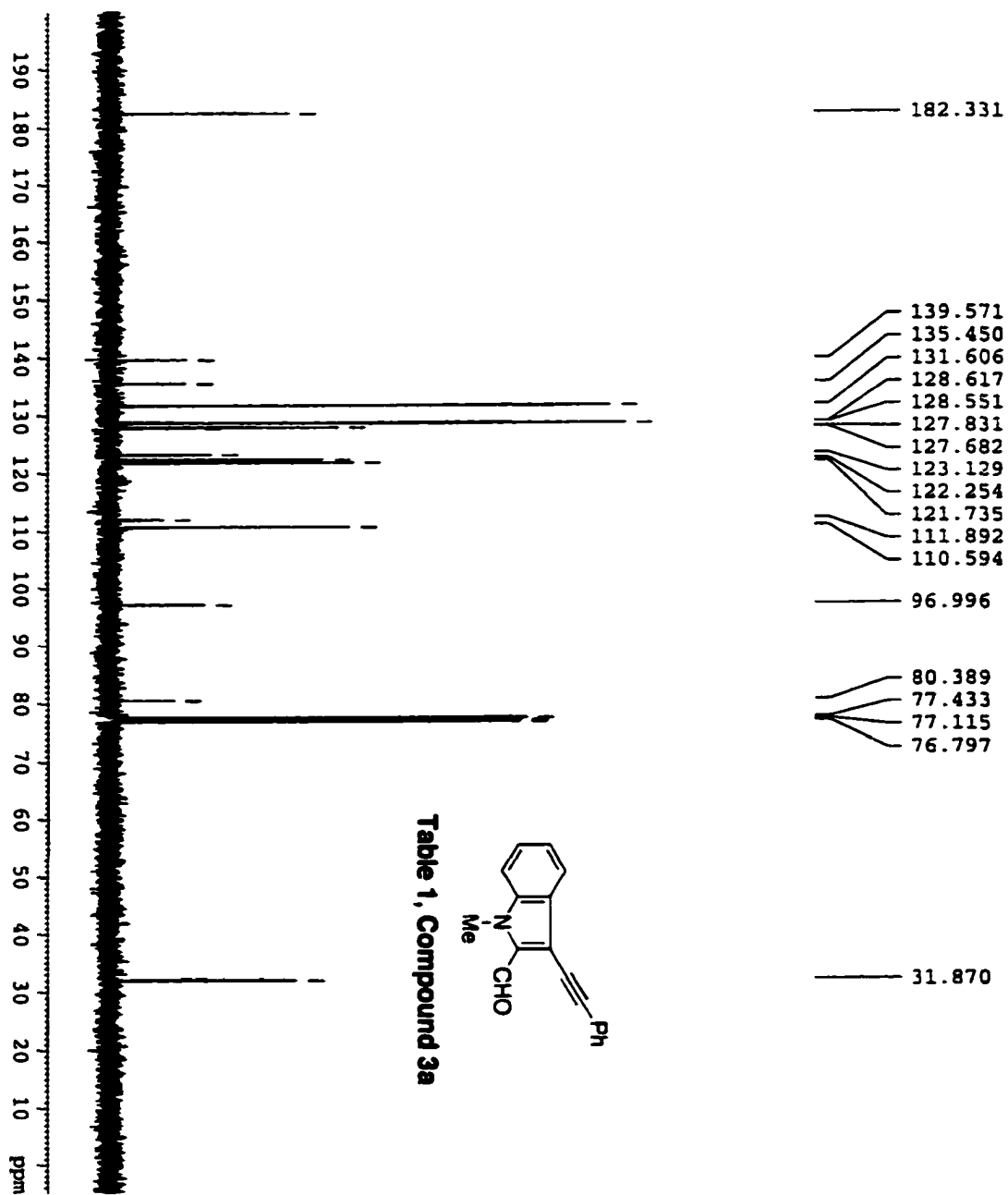


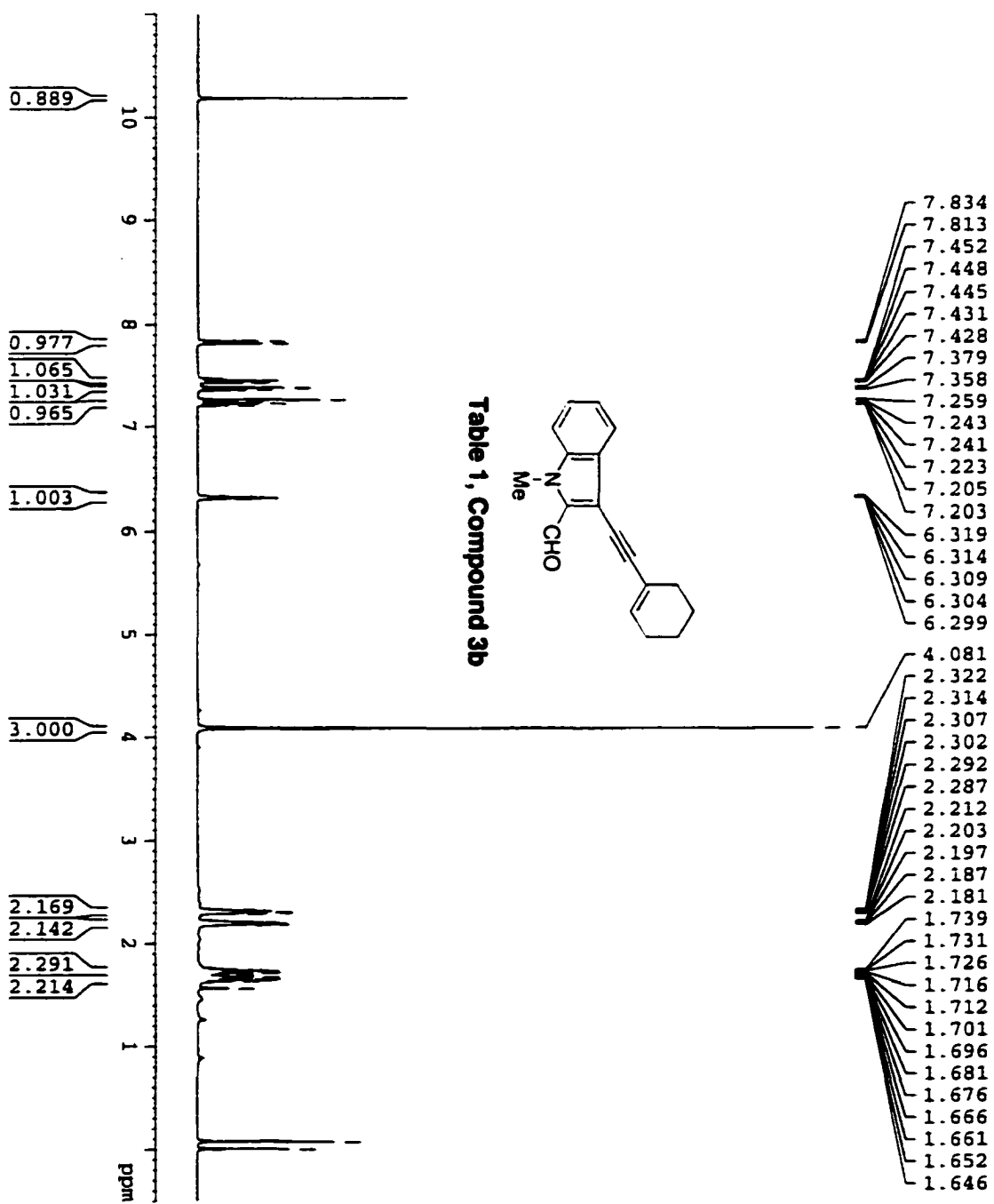


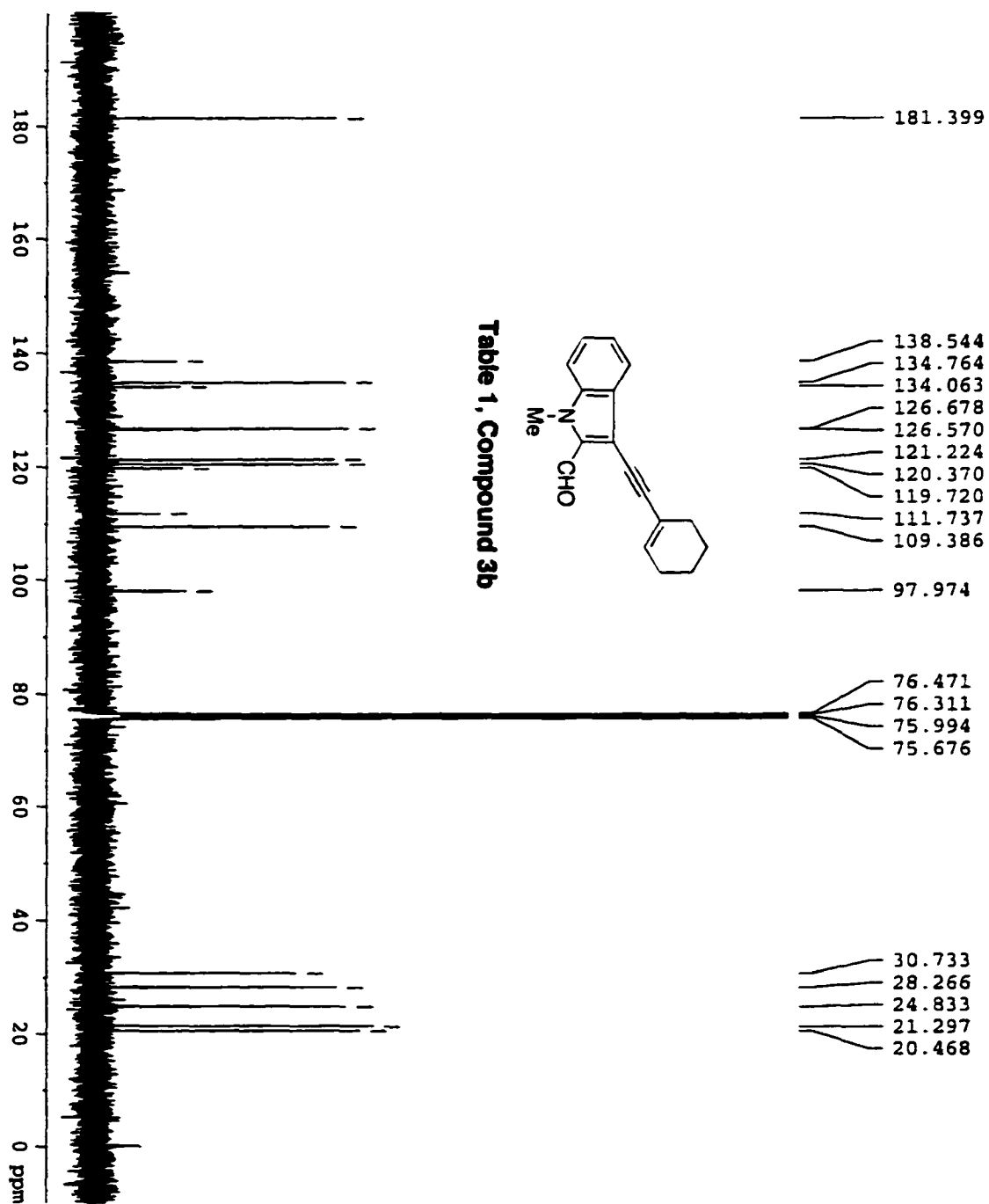
**APPENDIX B. CHAPTER 2  $^1\text{H}$  AND  $^{13}\text{C}$  NMR SPECTRA**

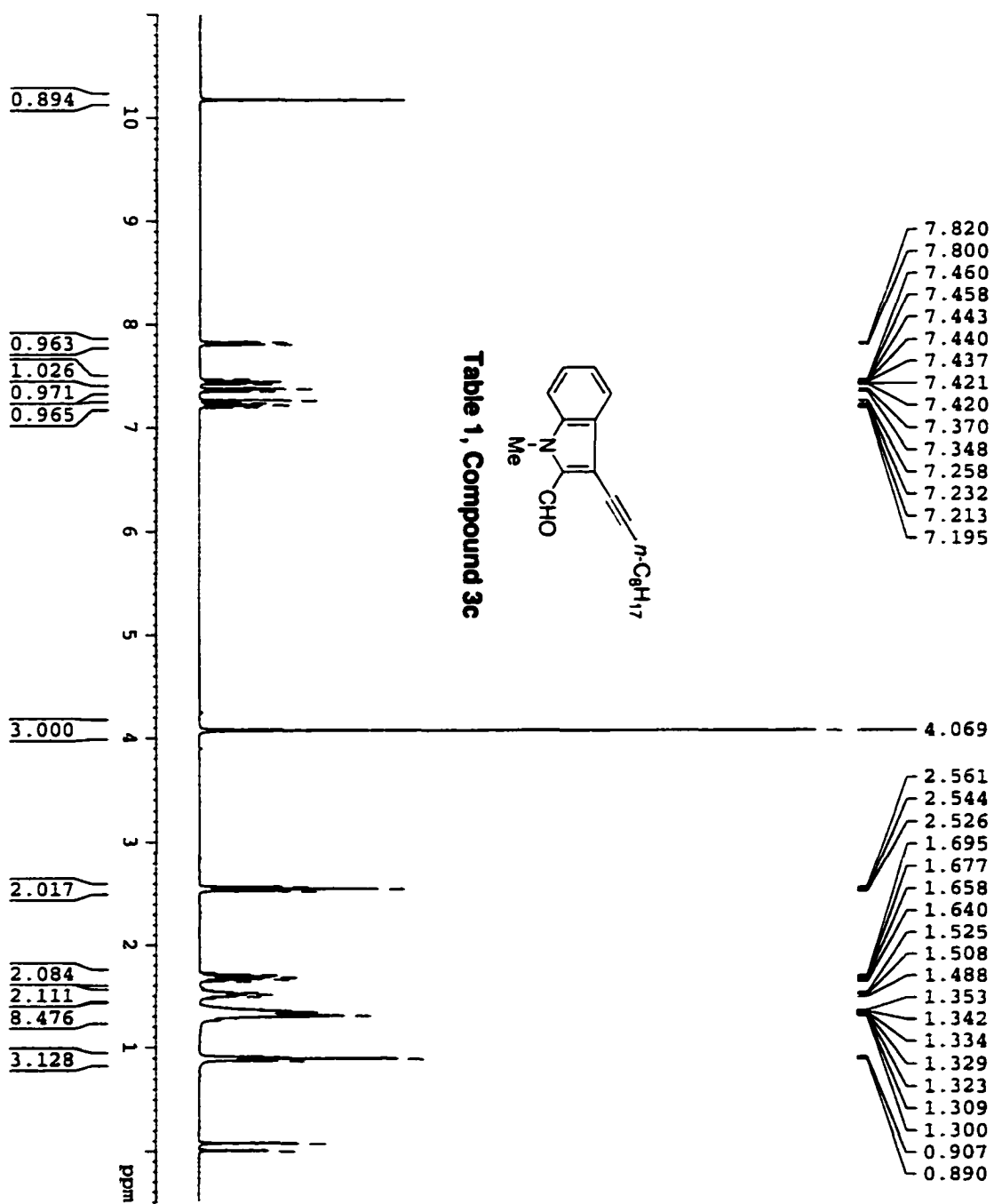


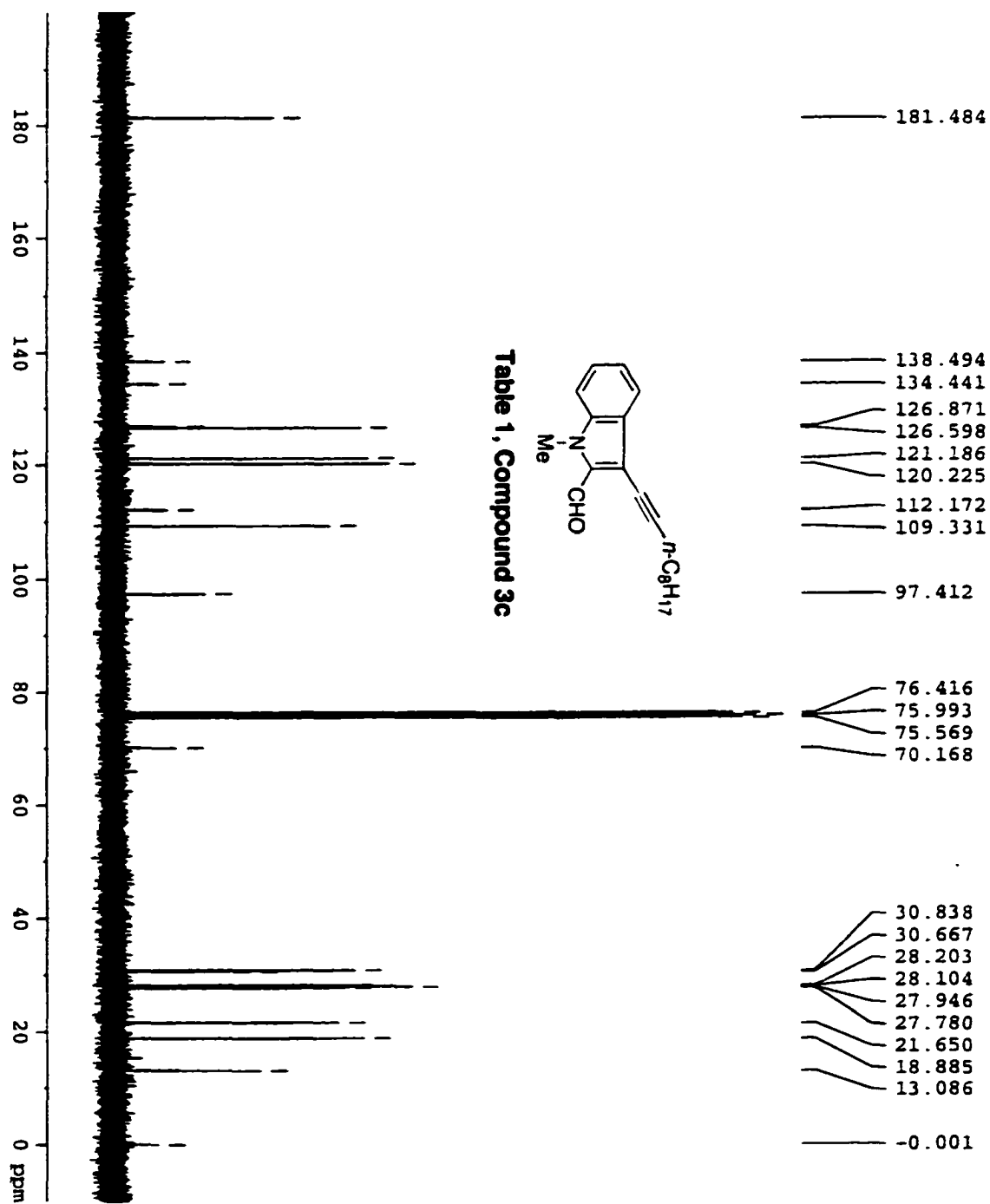


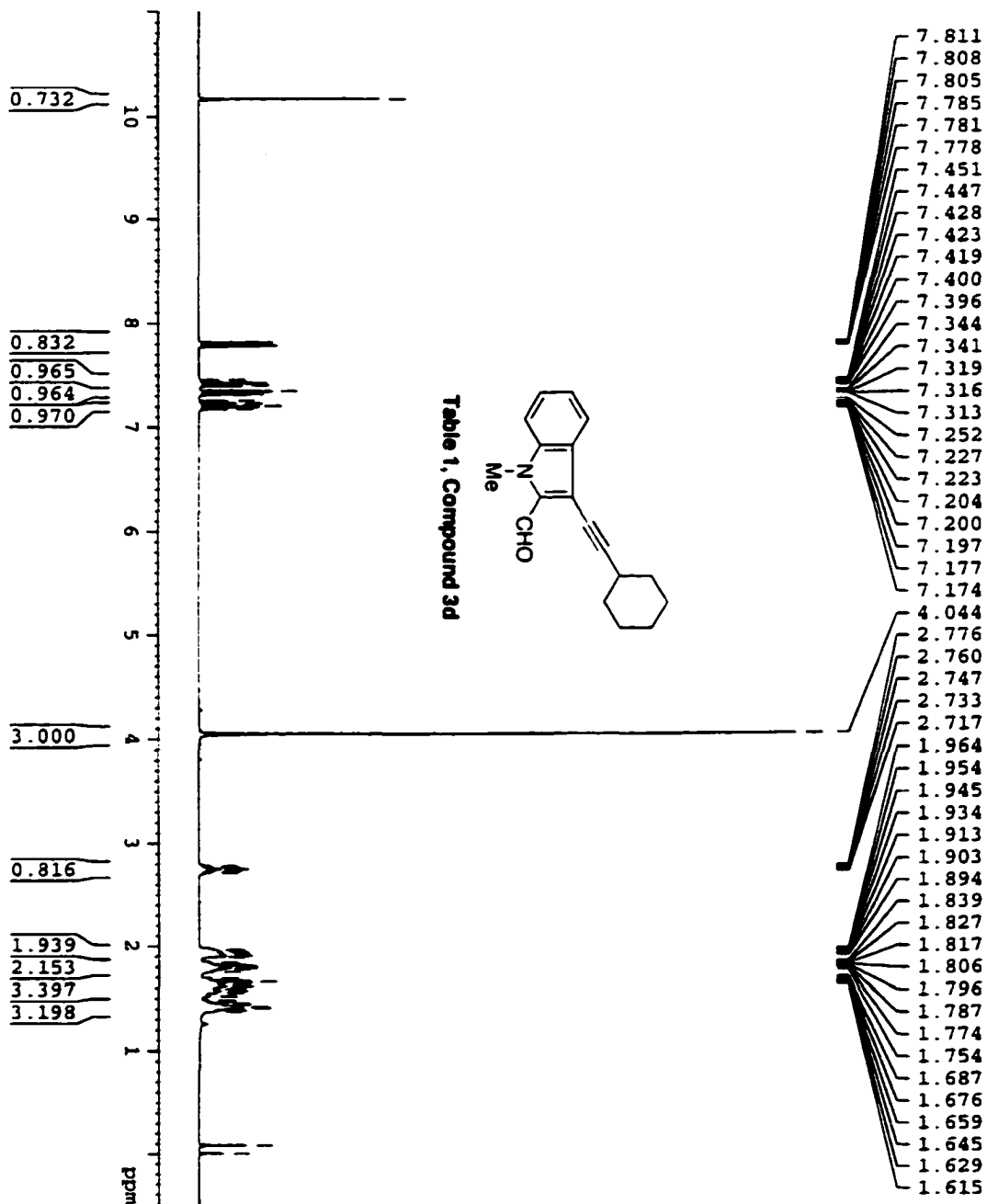


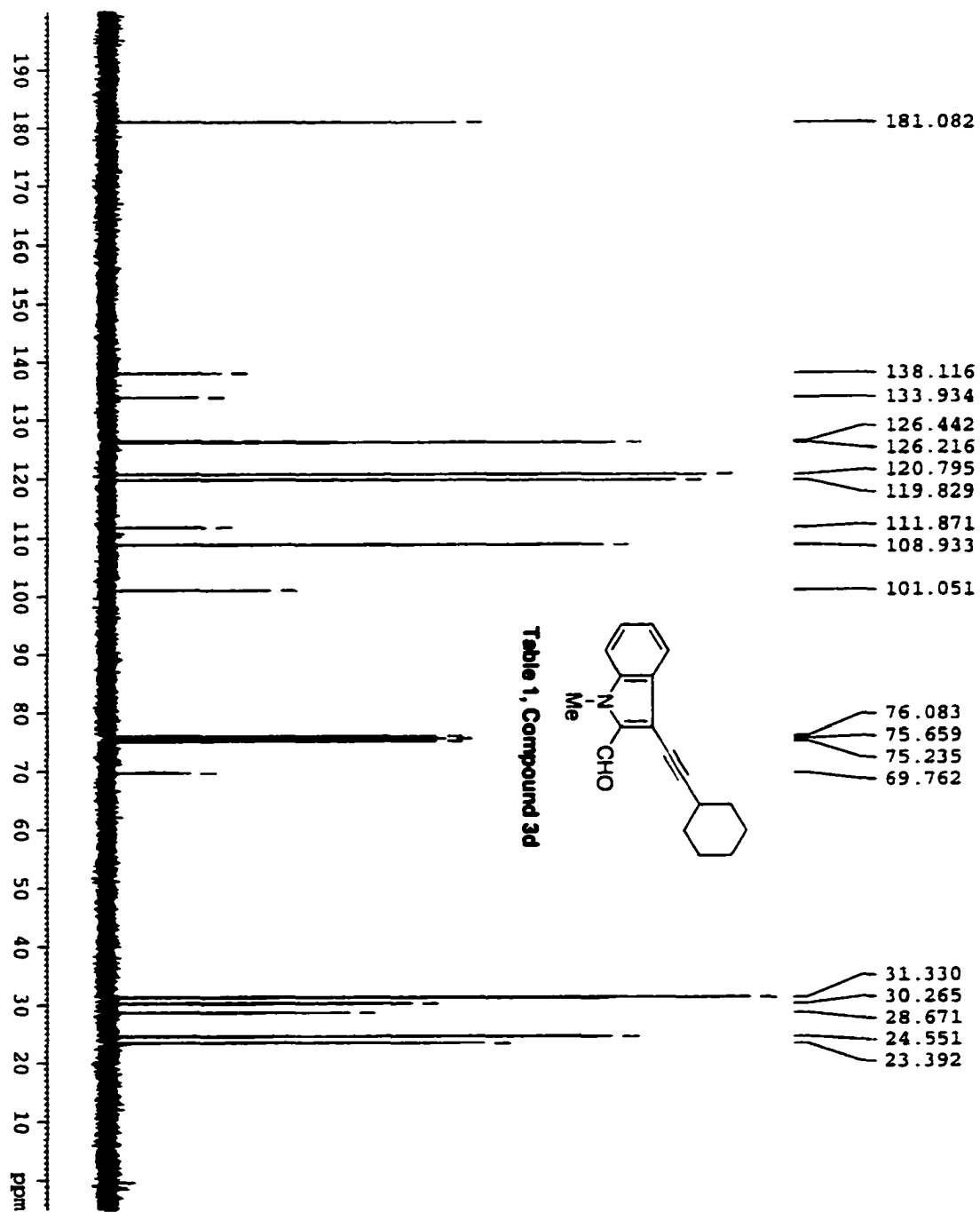




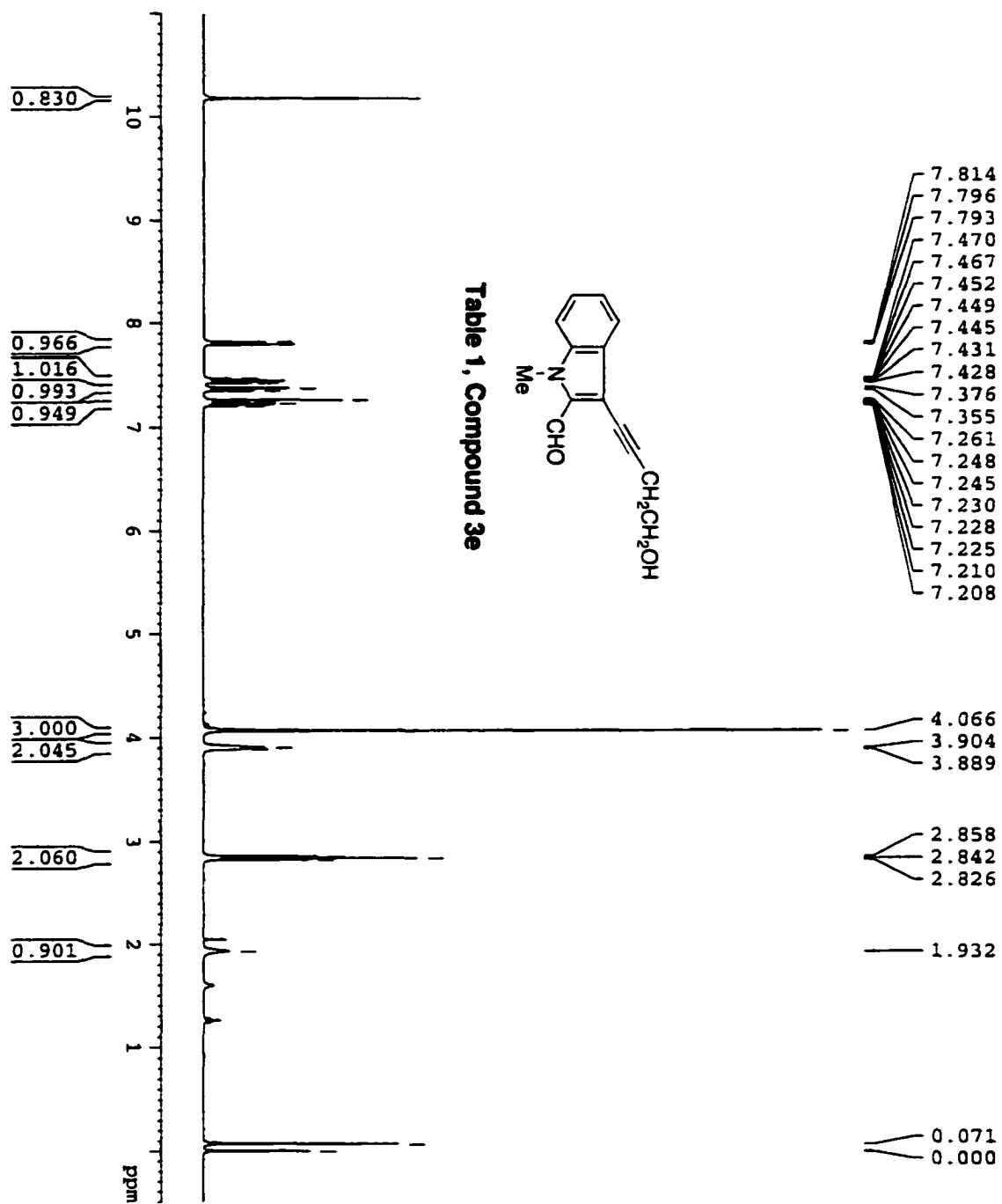


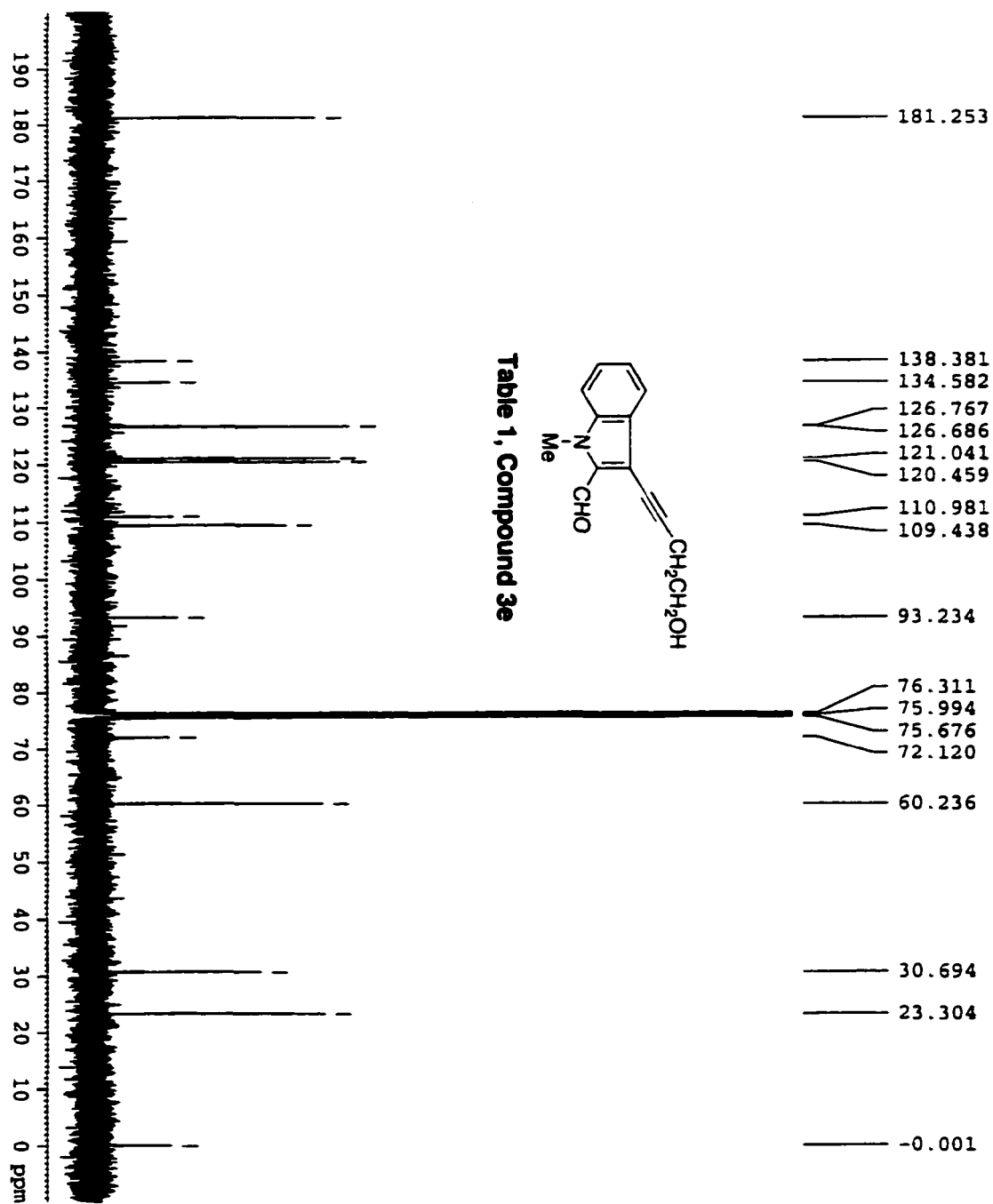


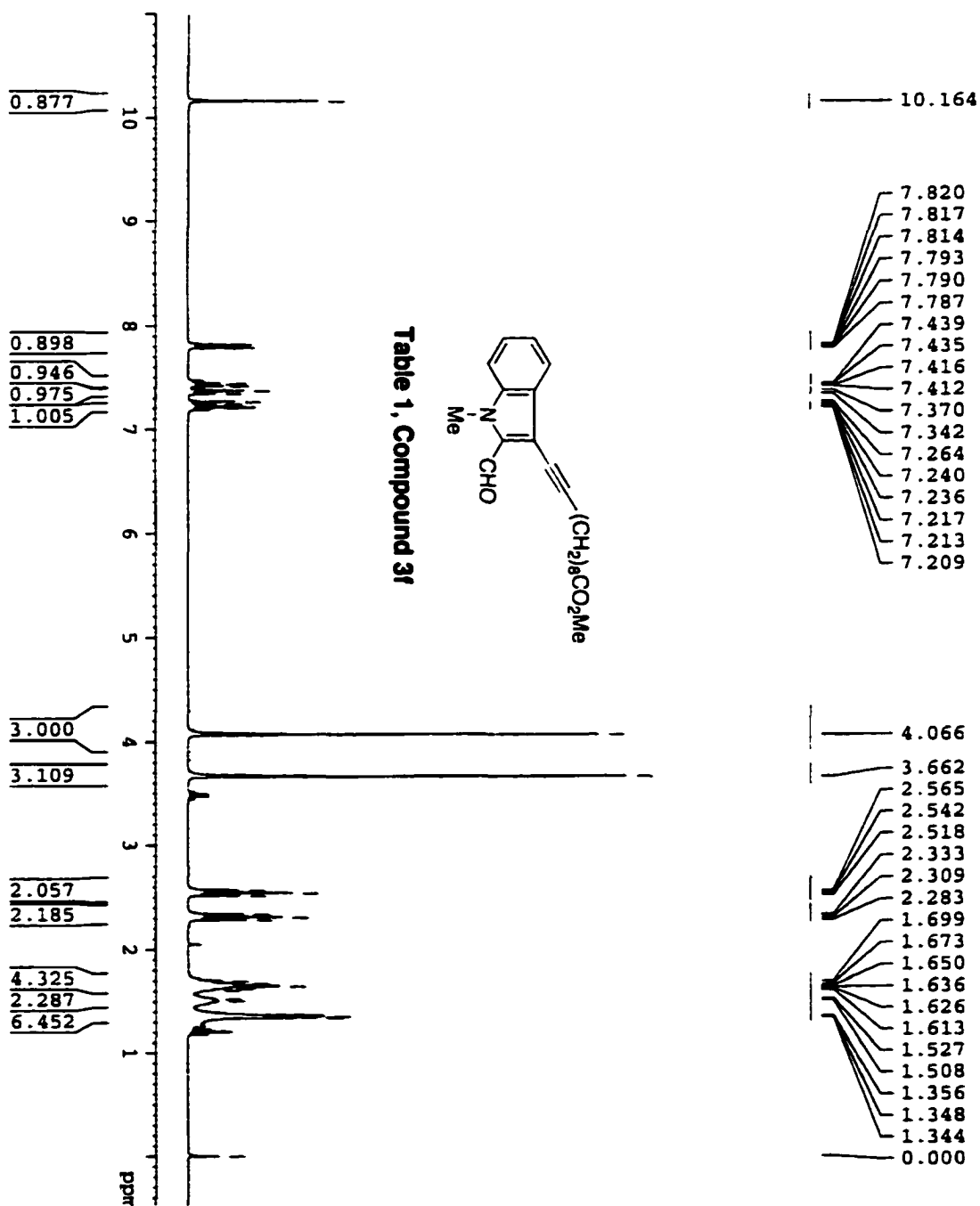


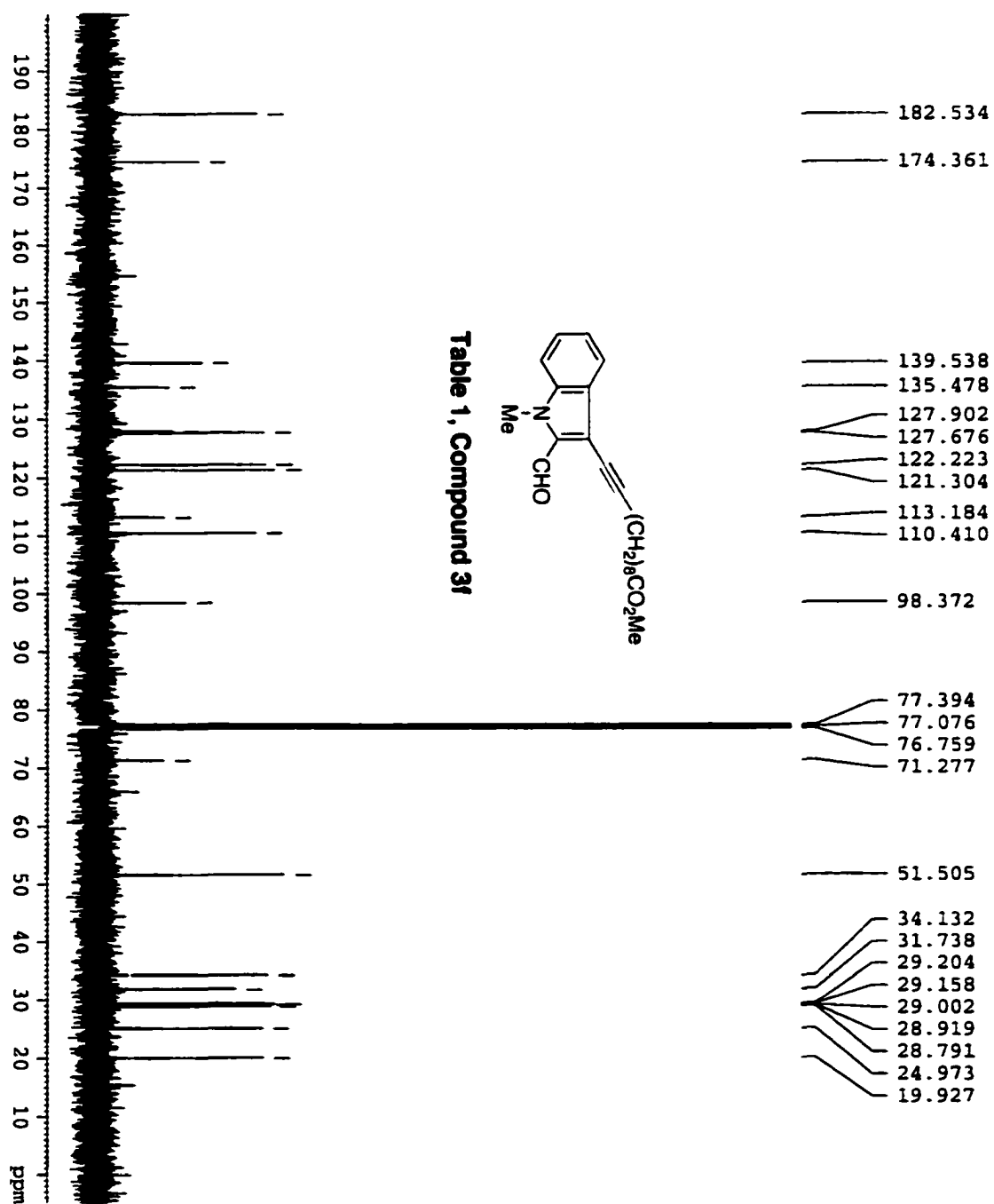


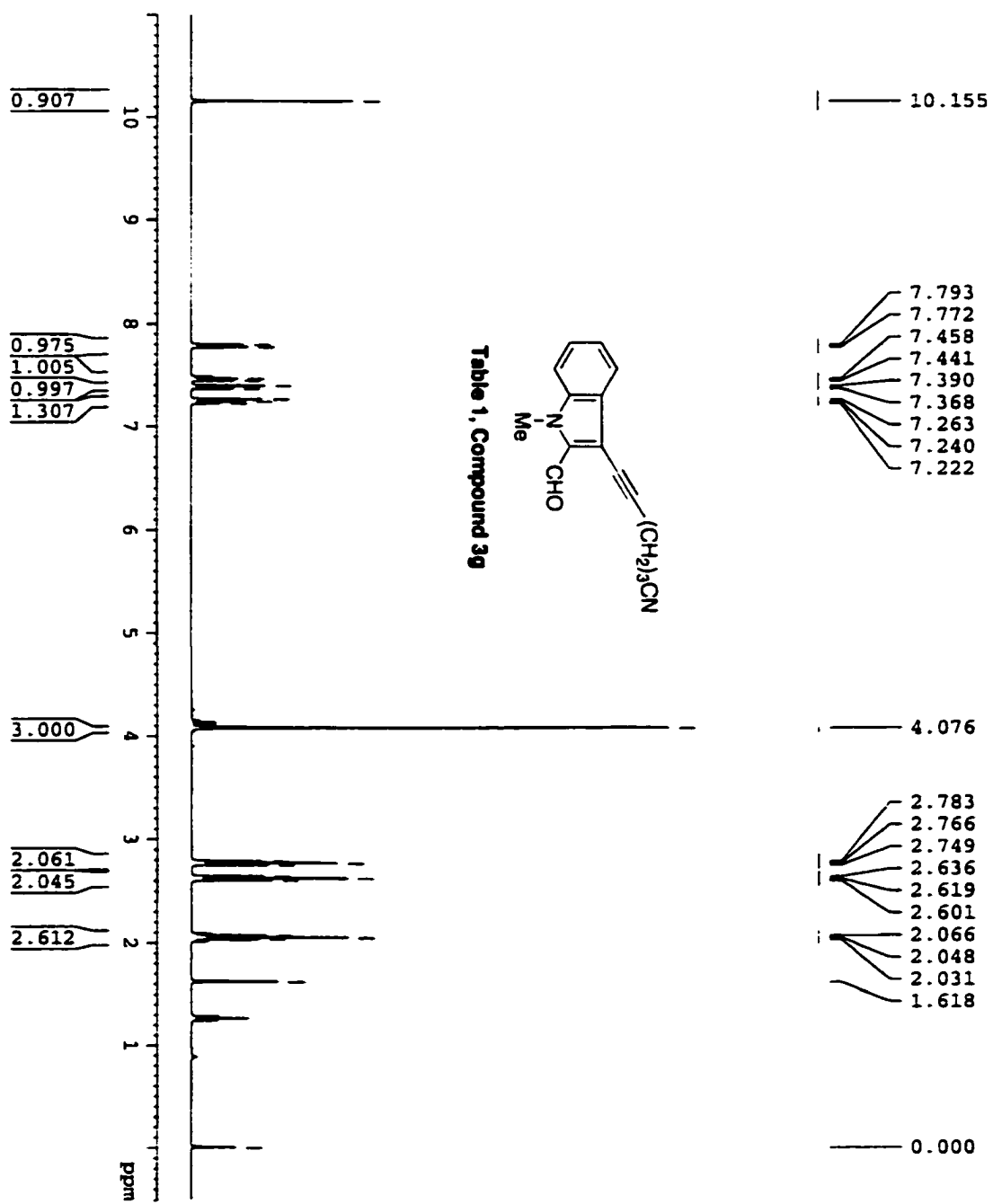


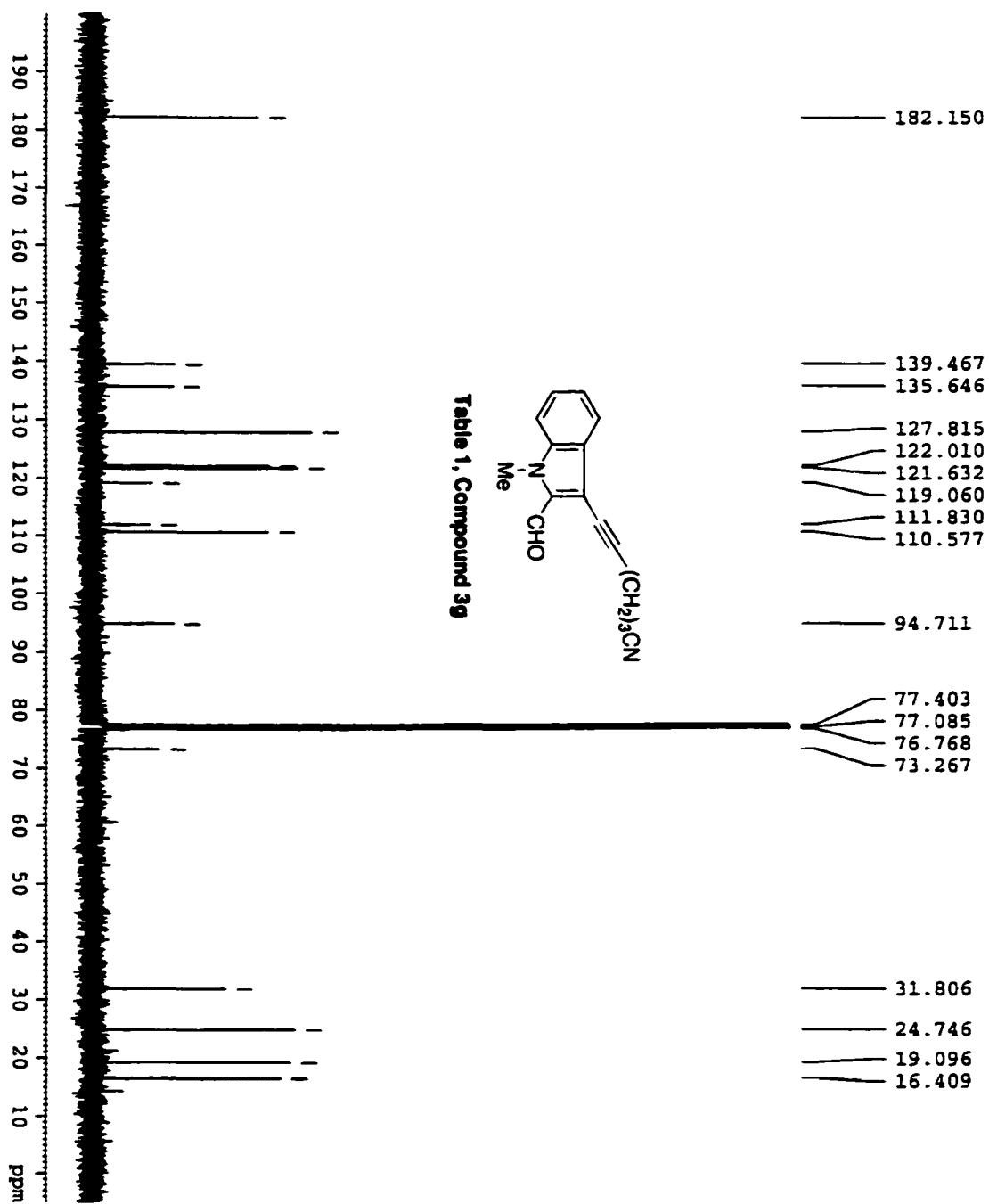


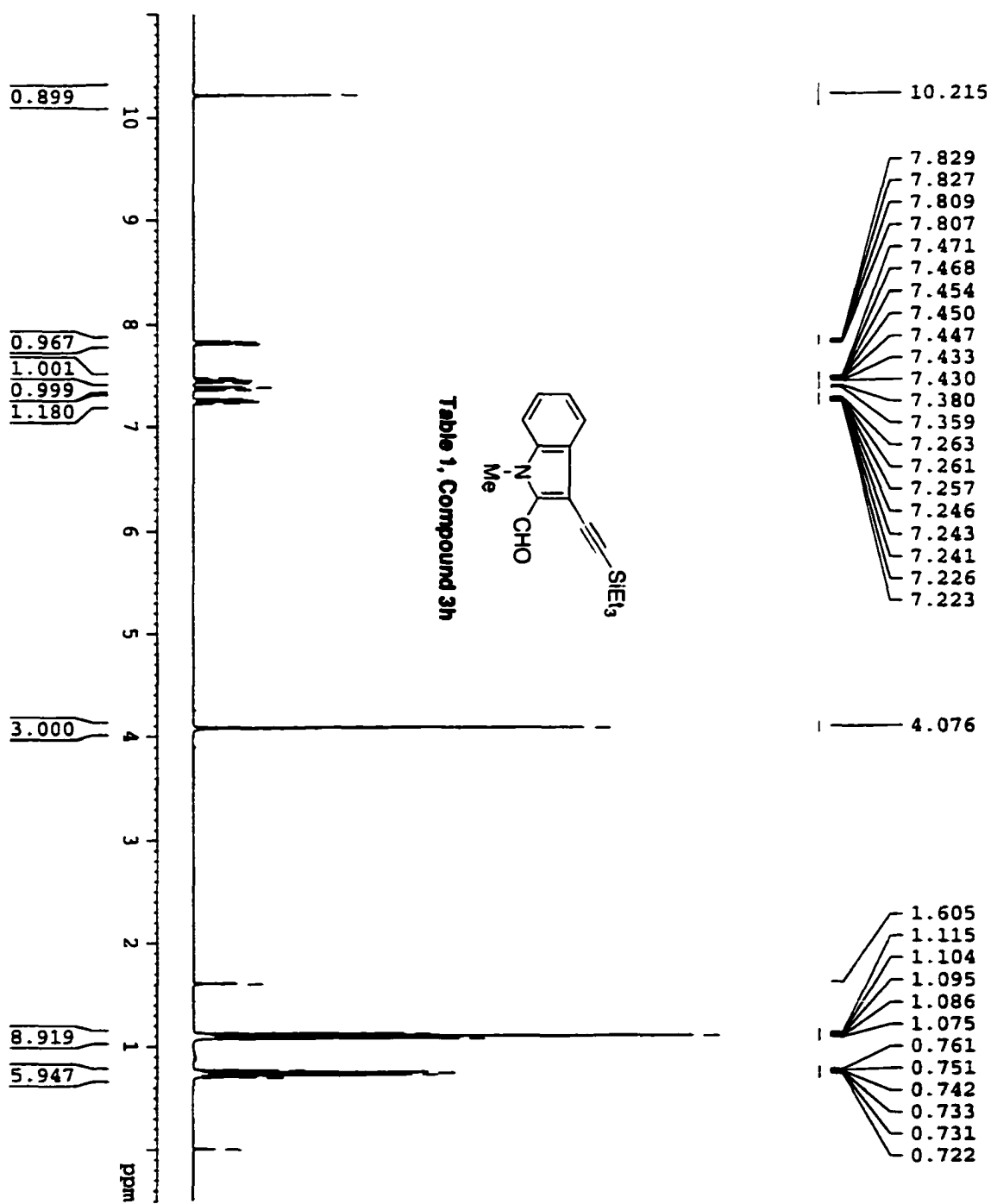


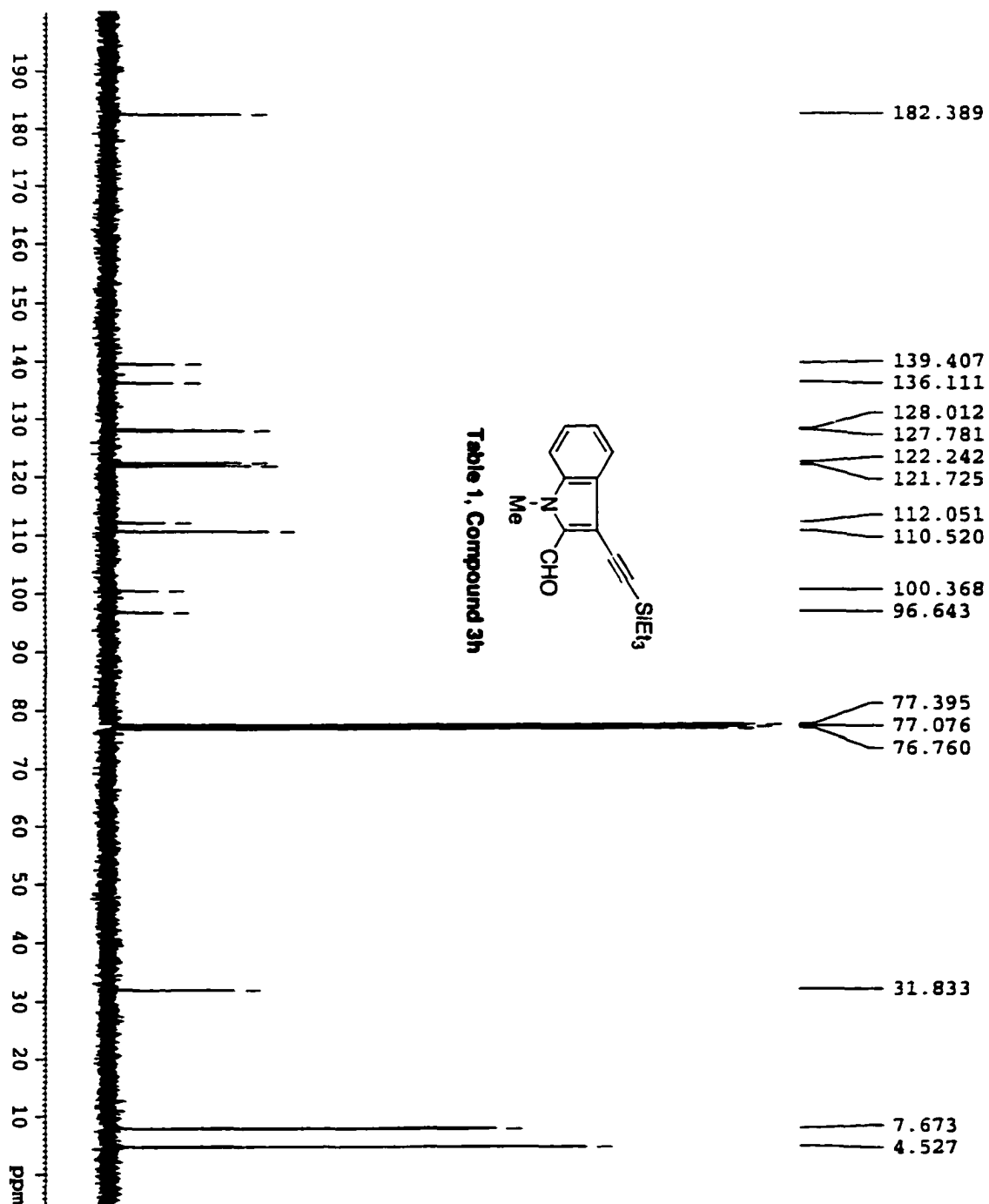




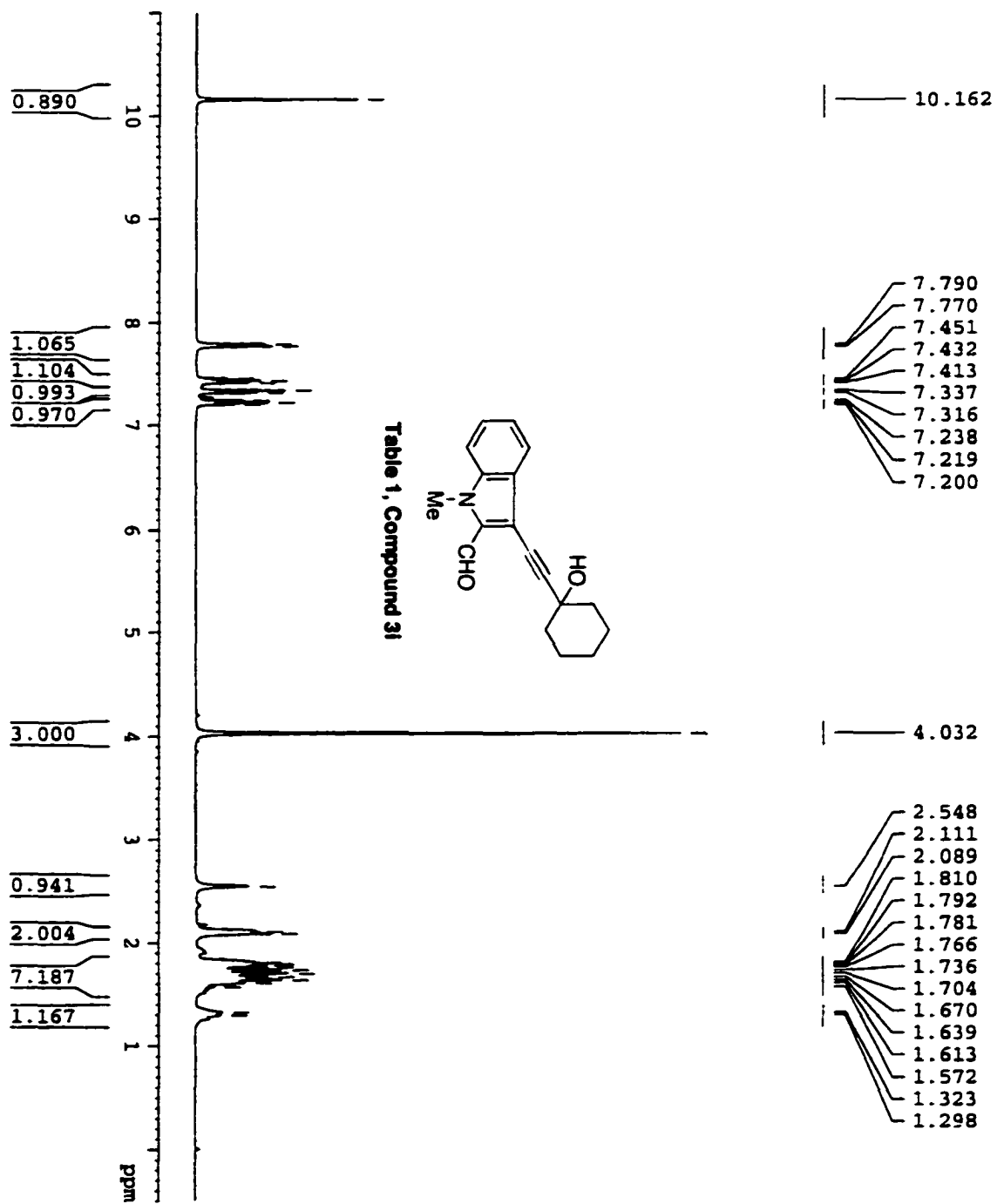


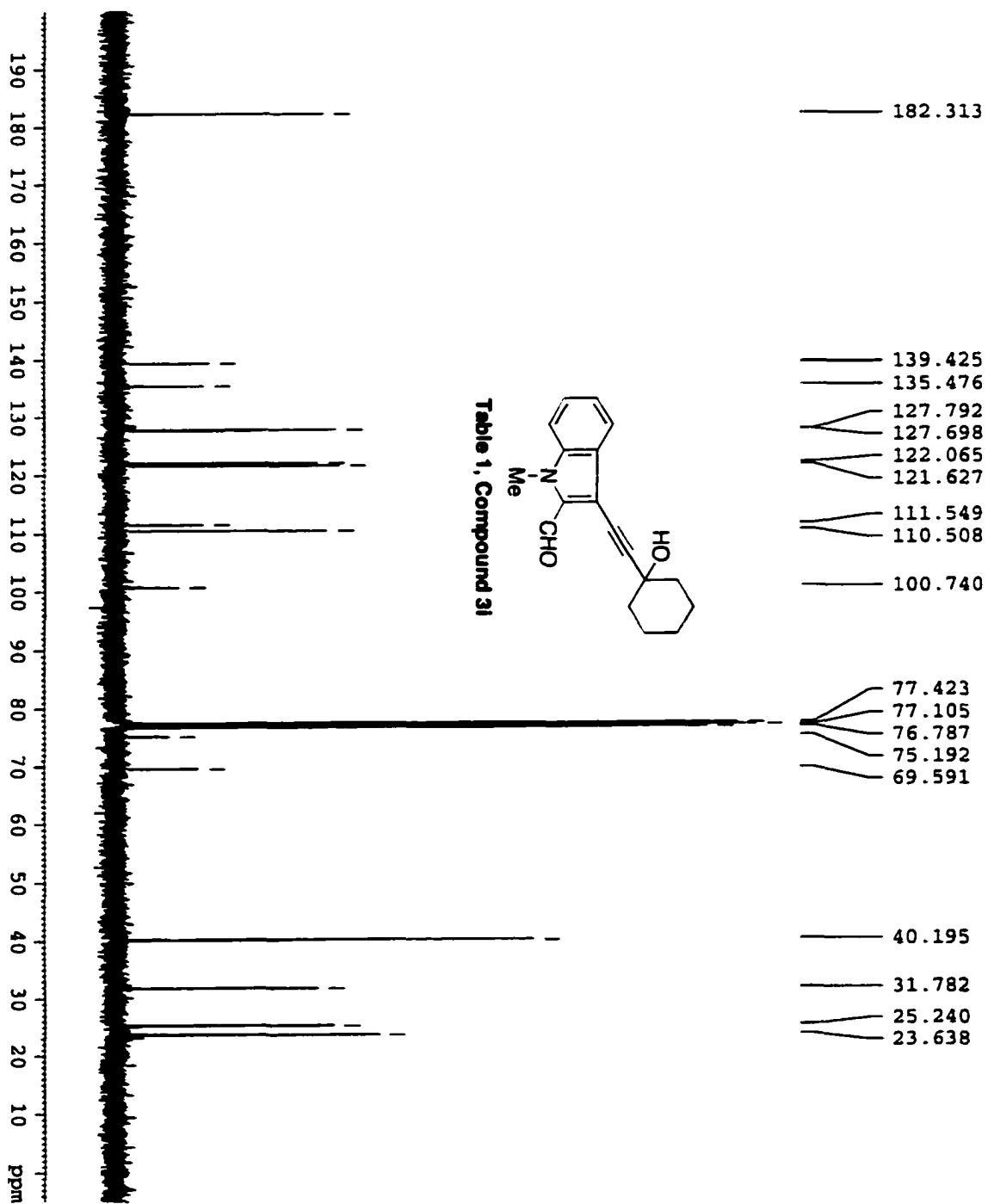


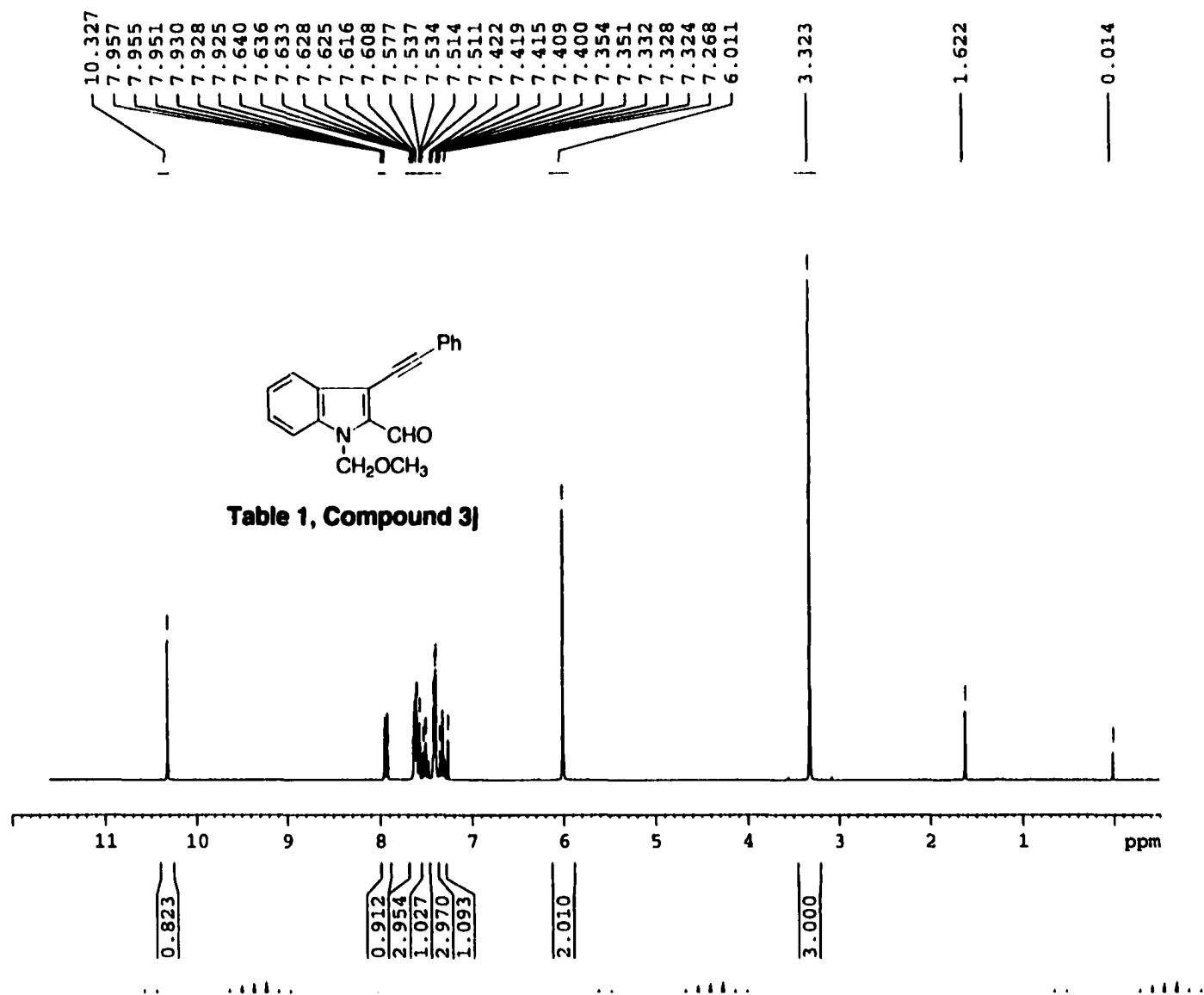


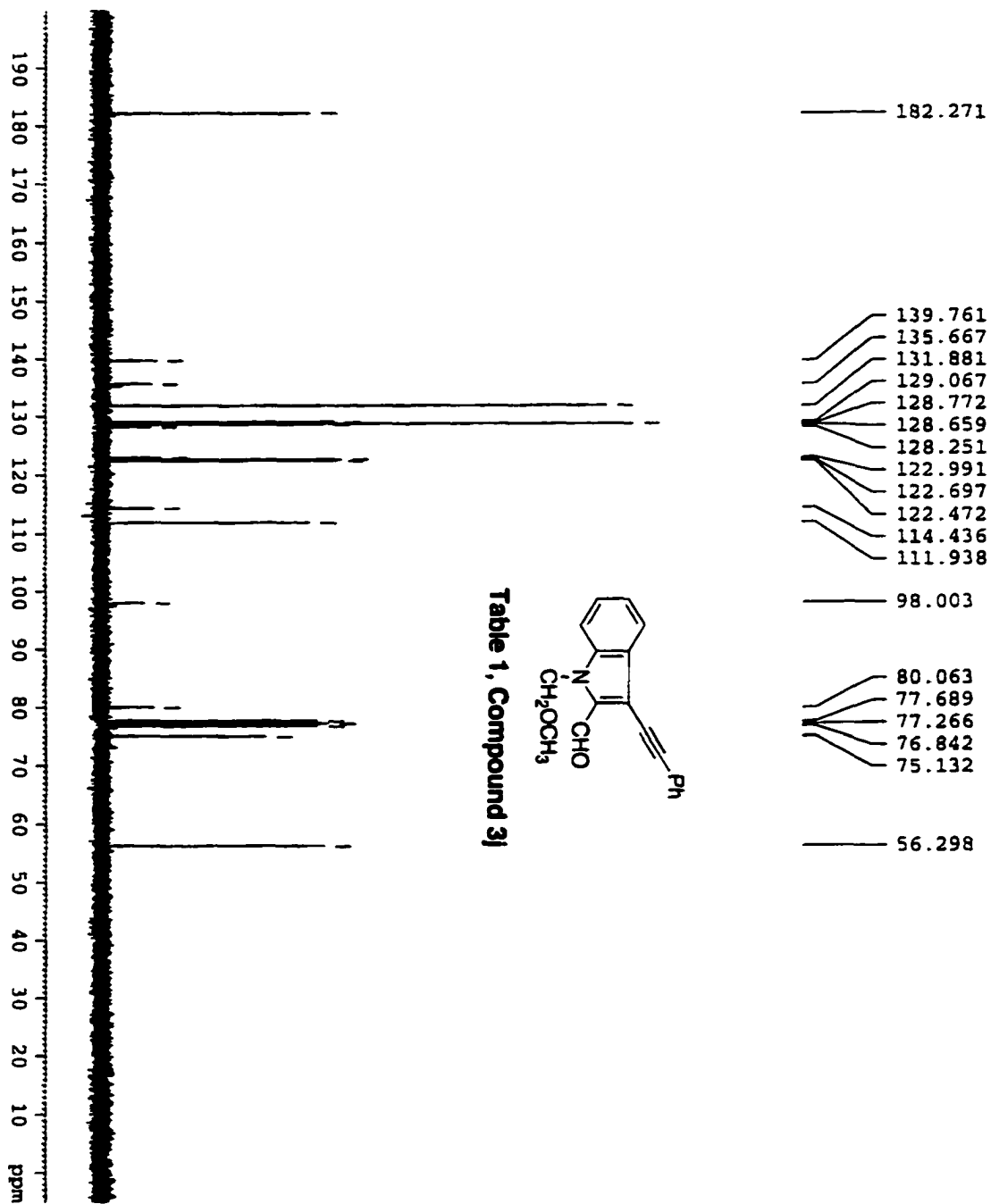


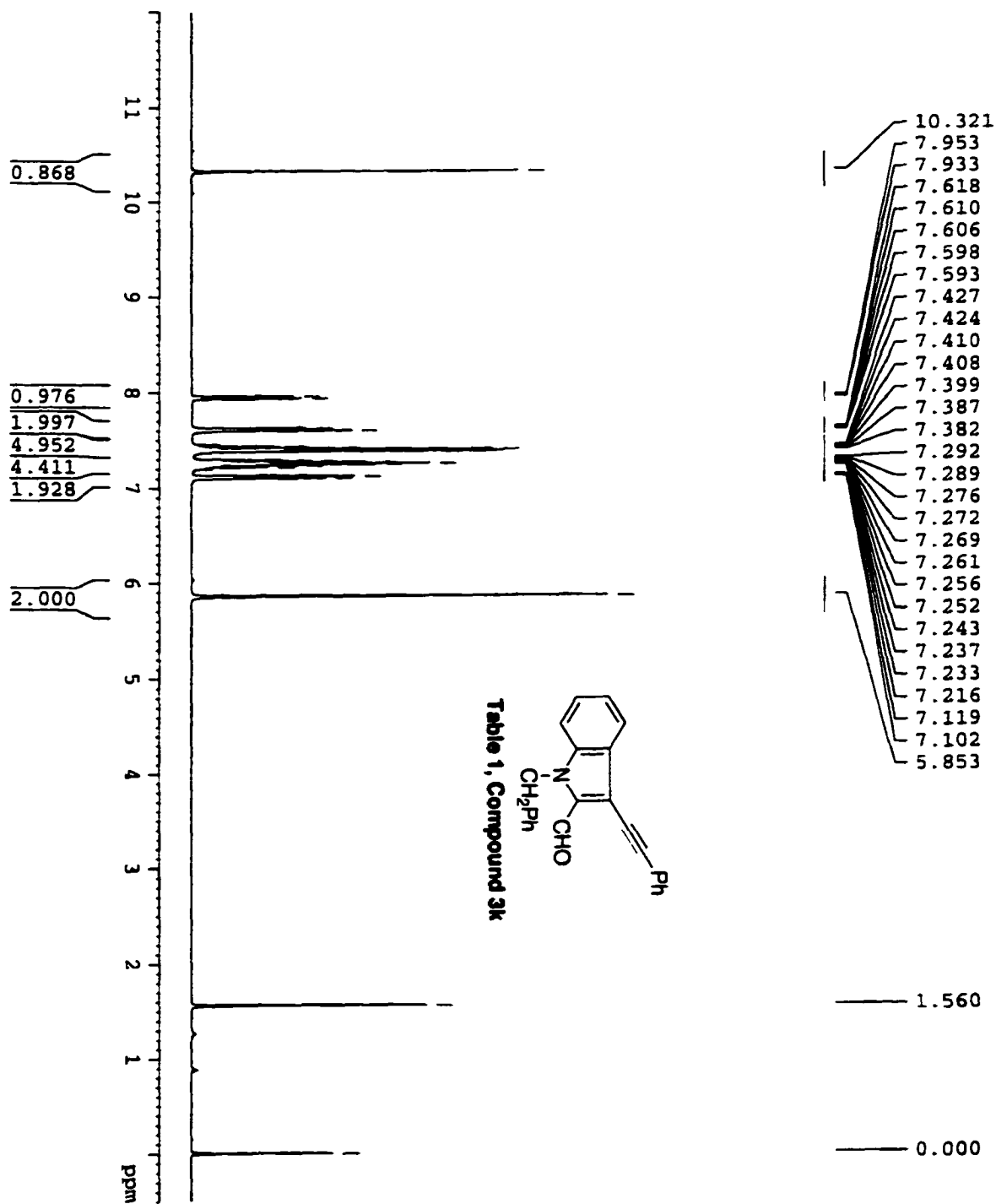


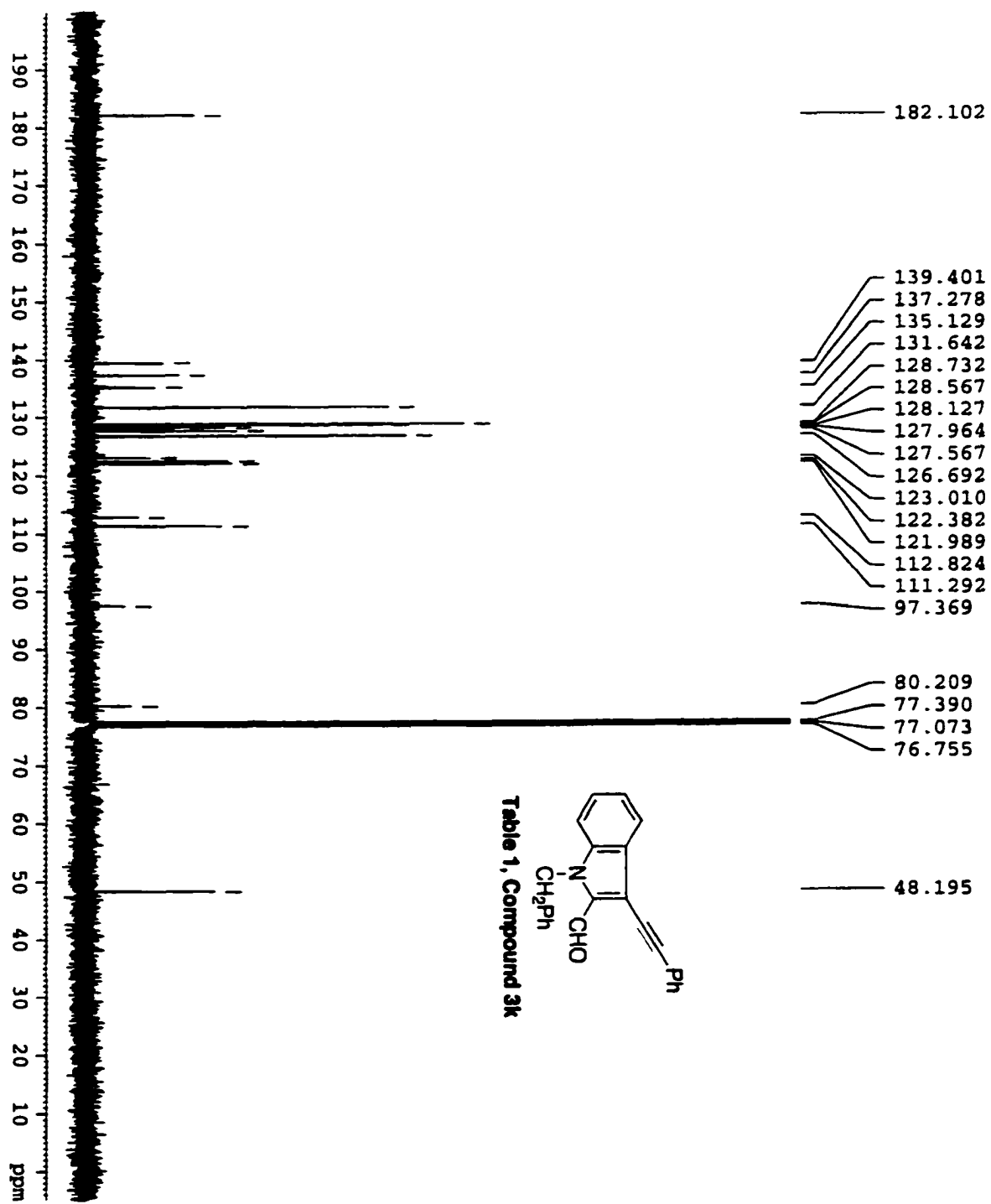


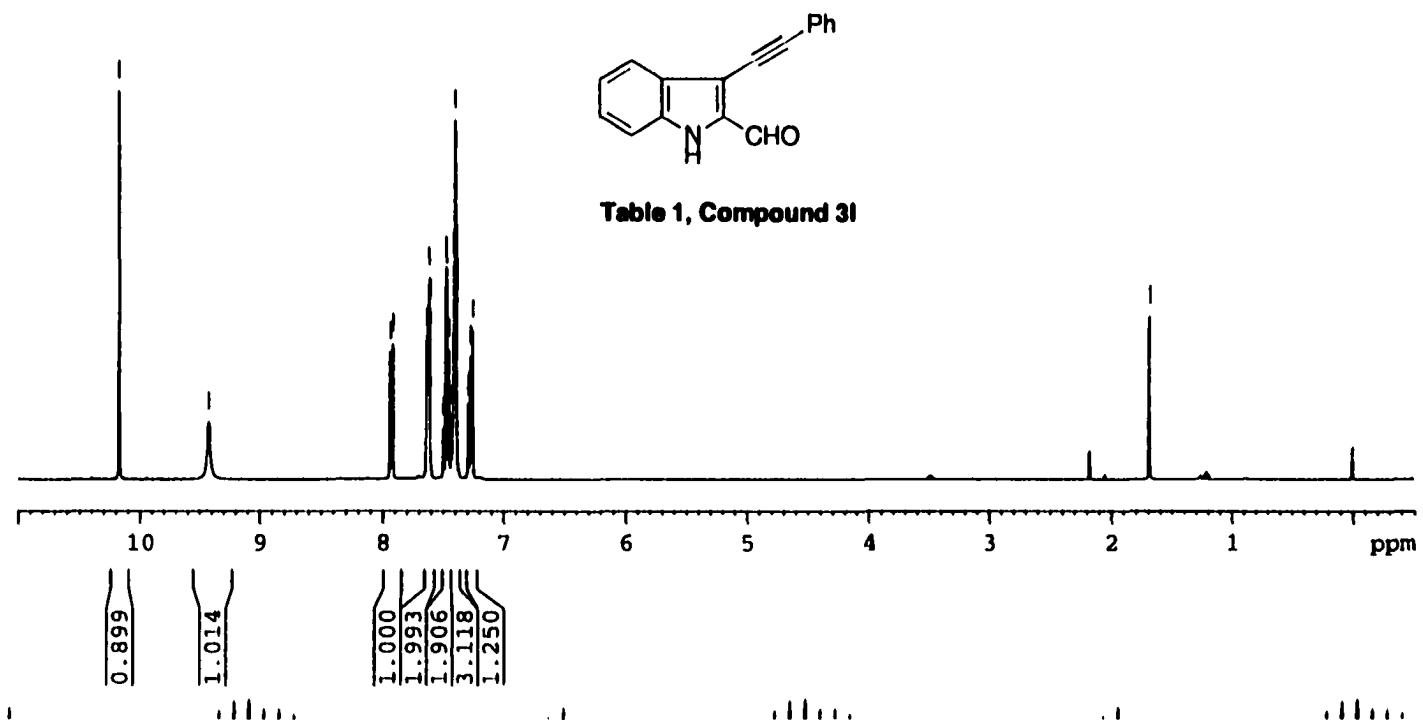


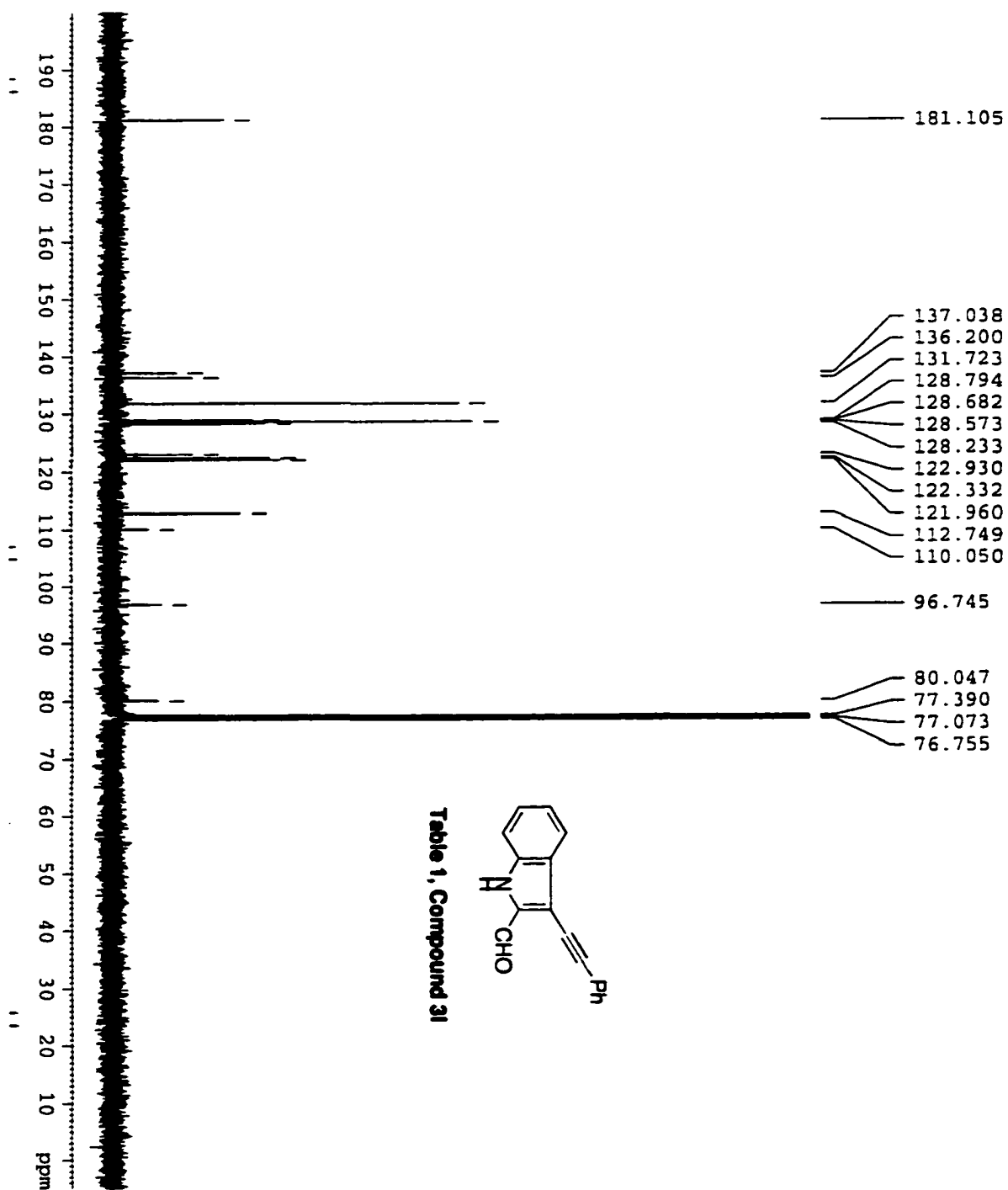




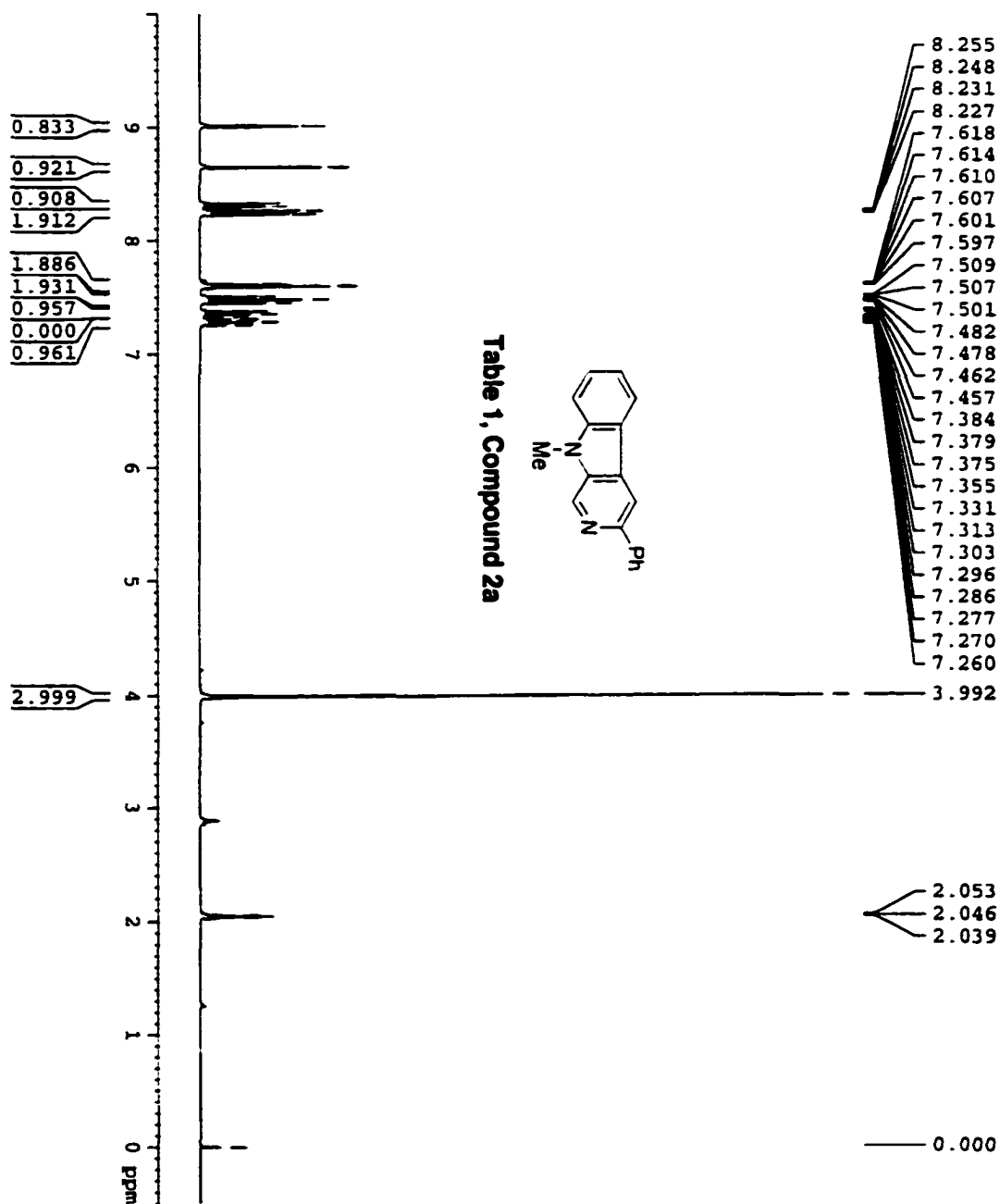


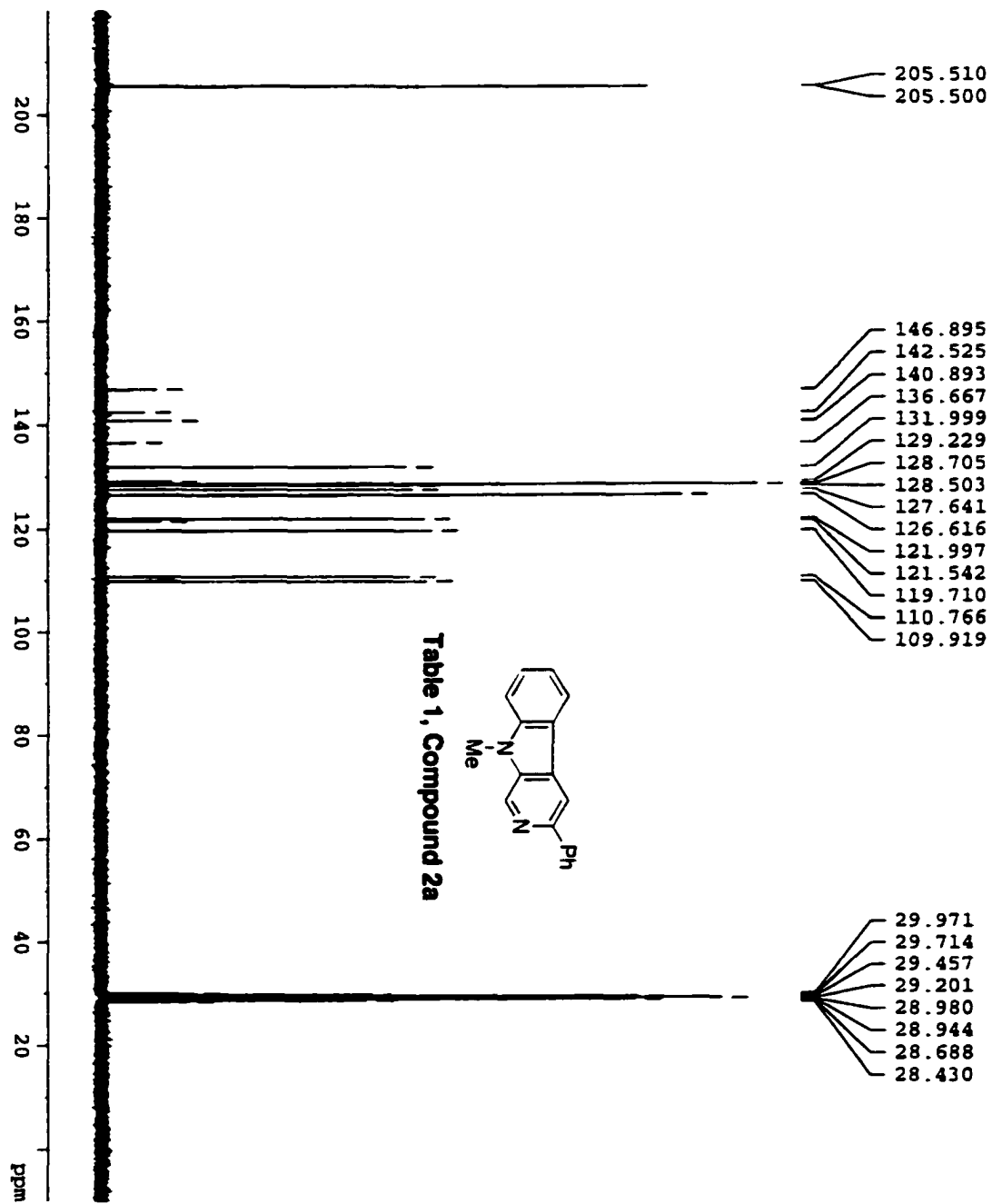


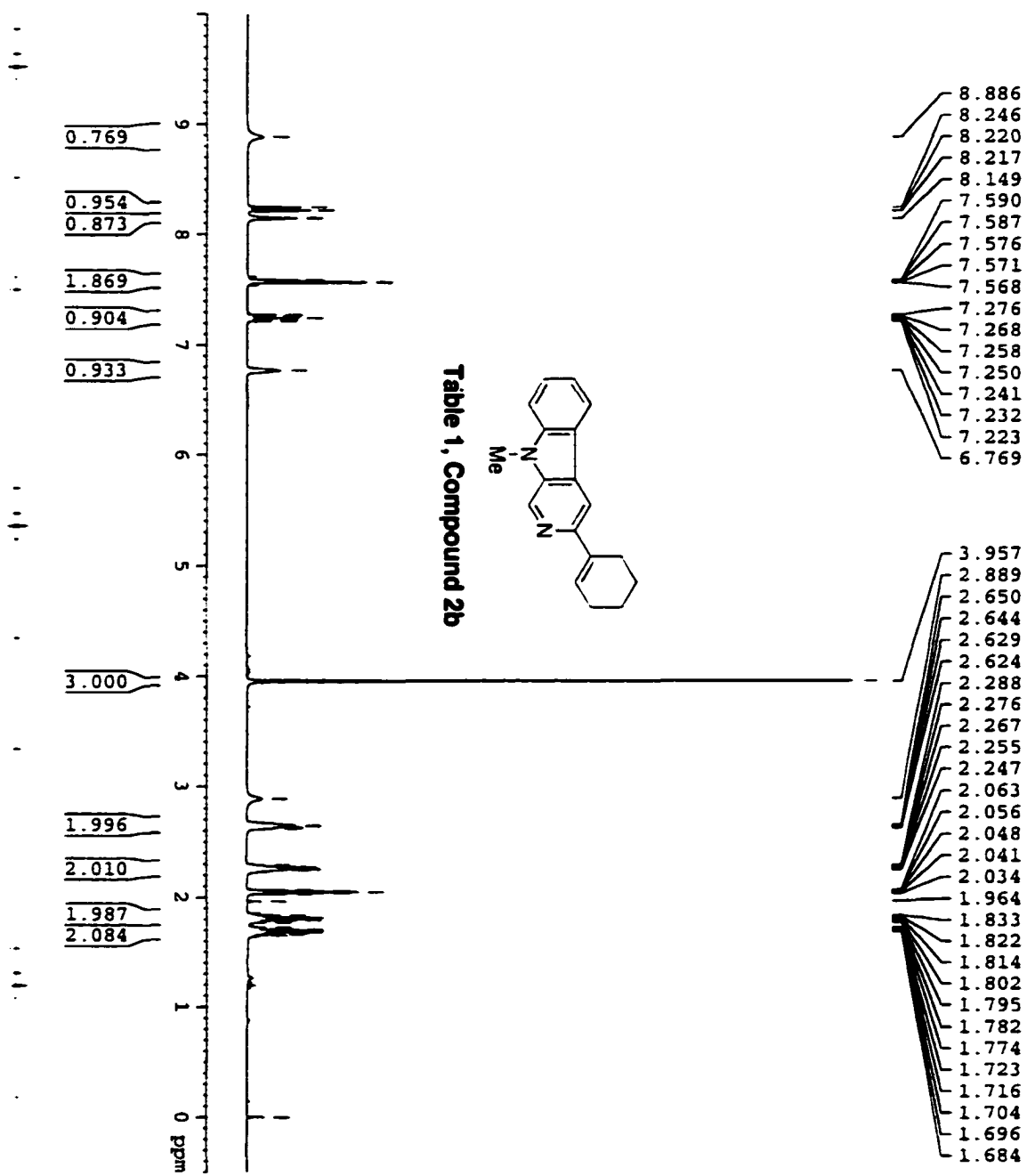


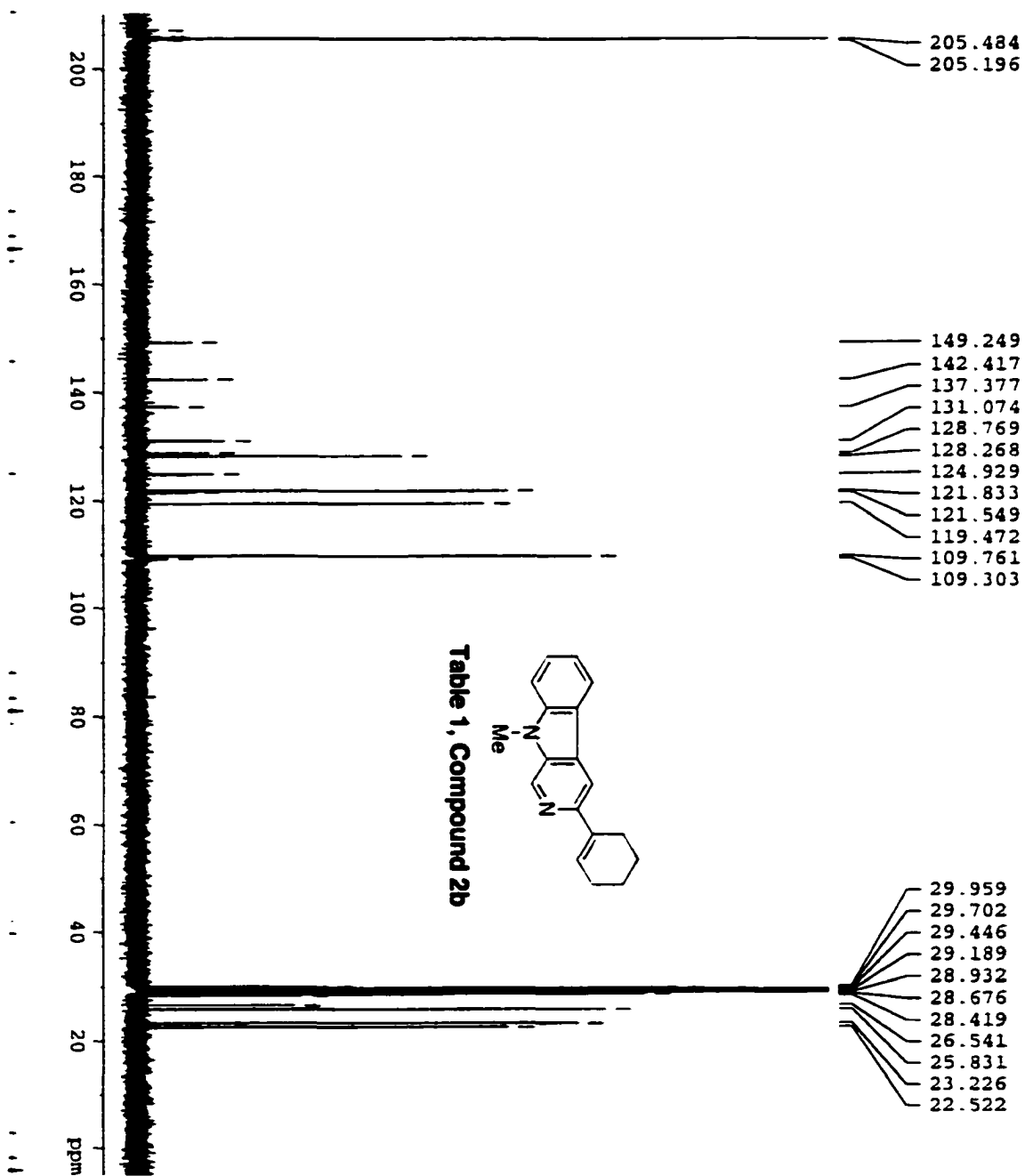


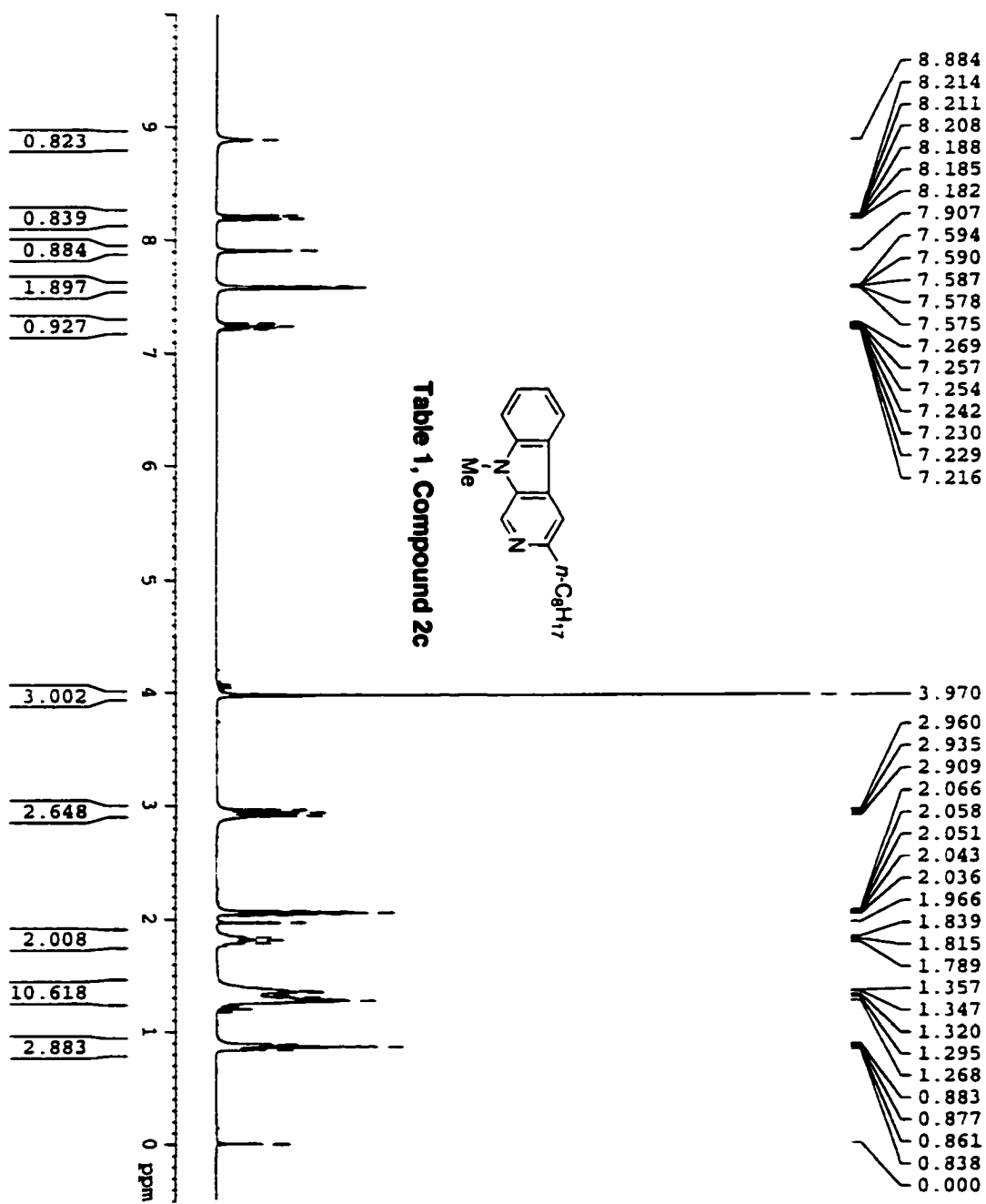


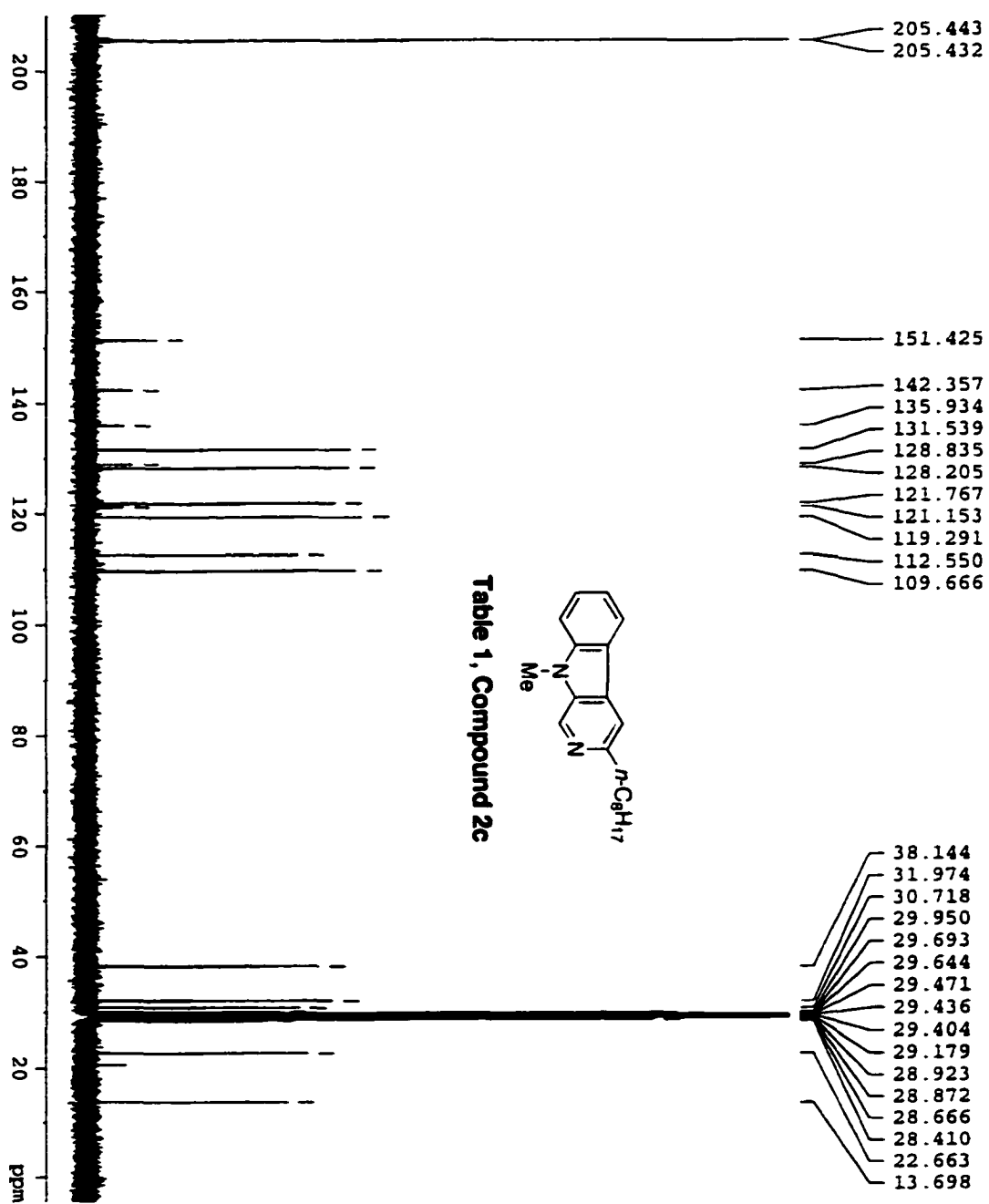


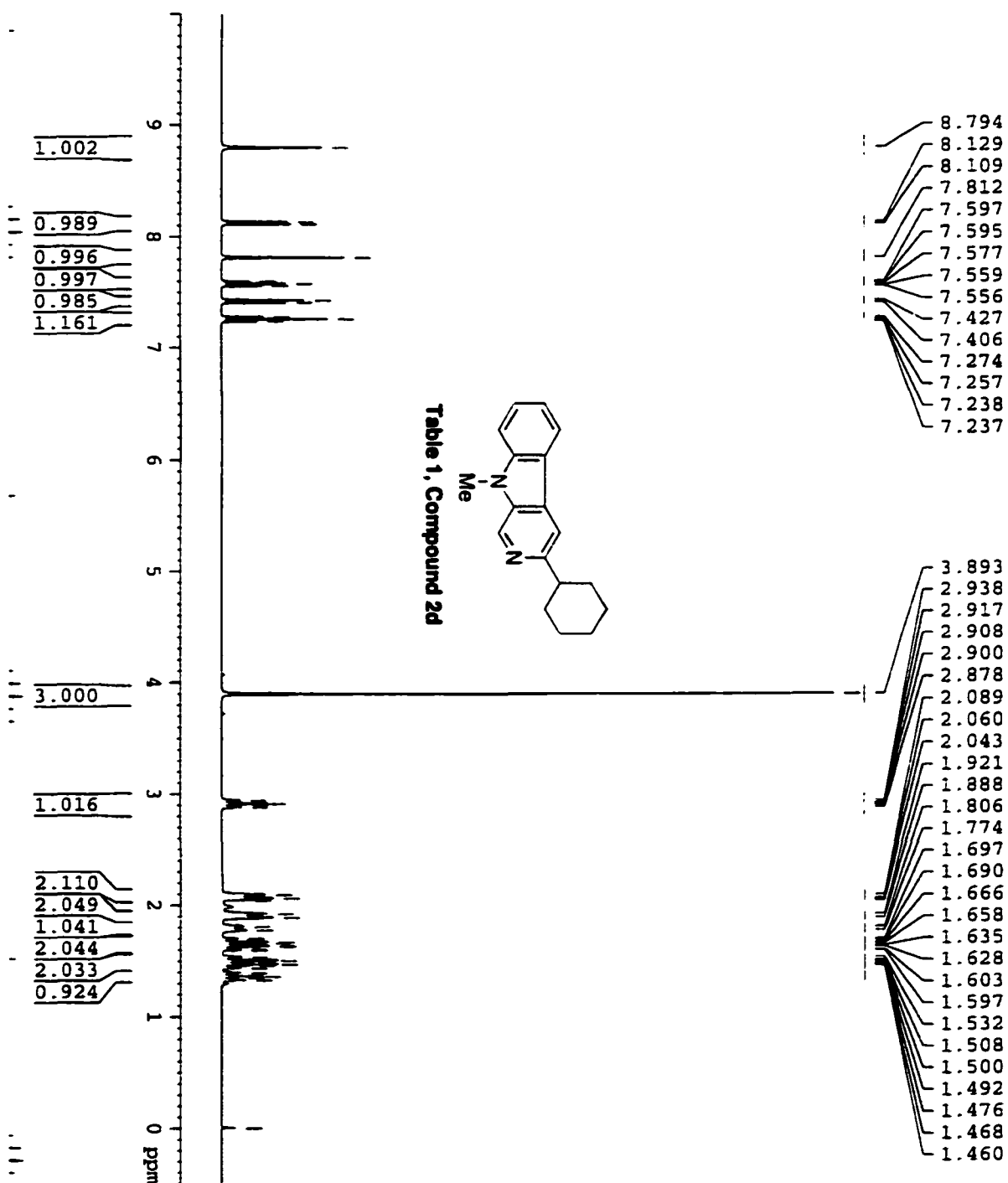


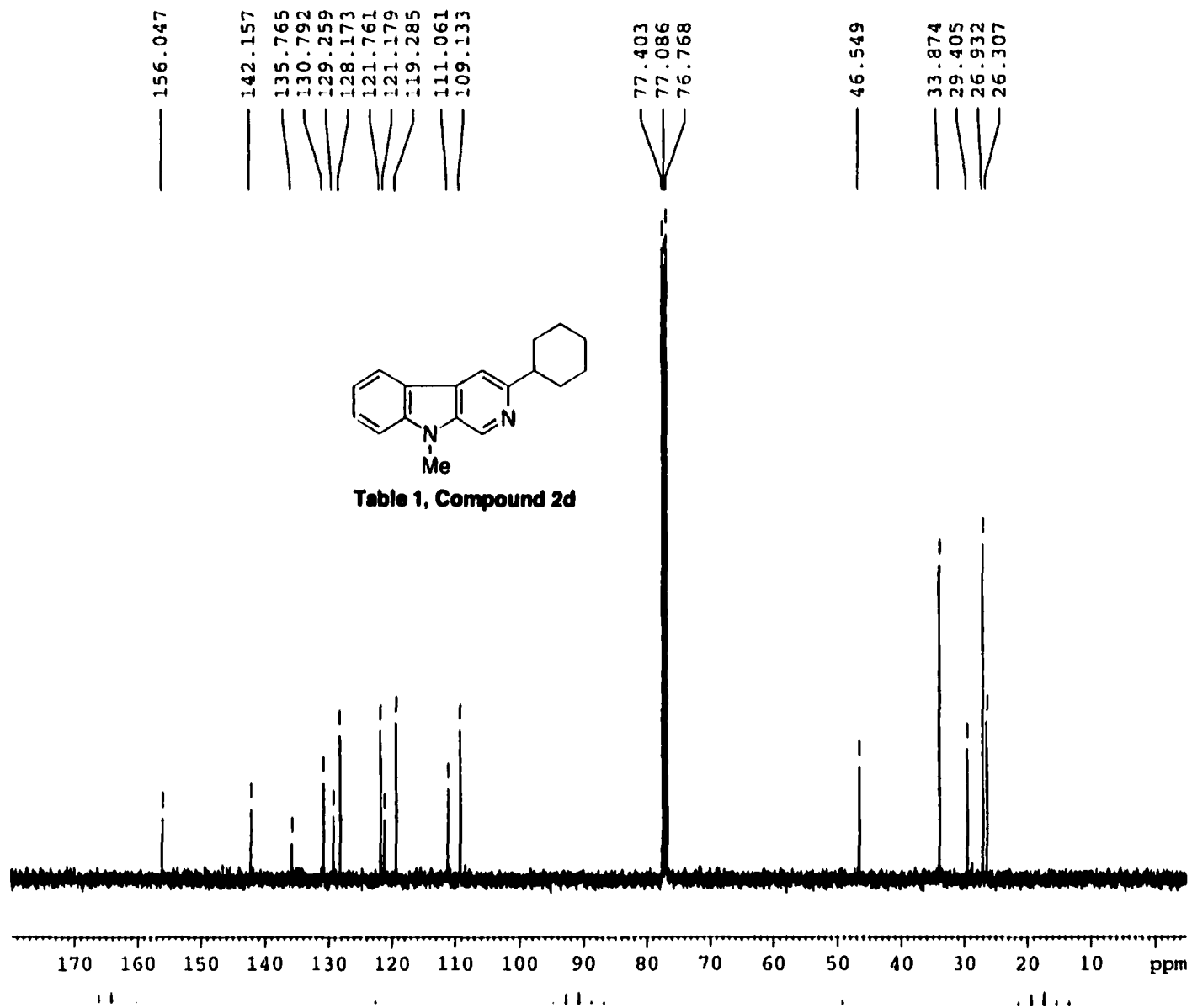




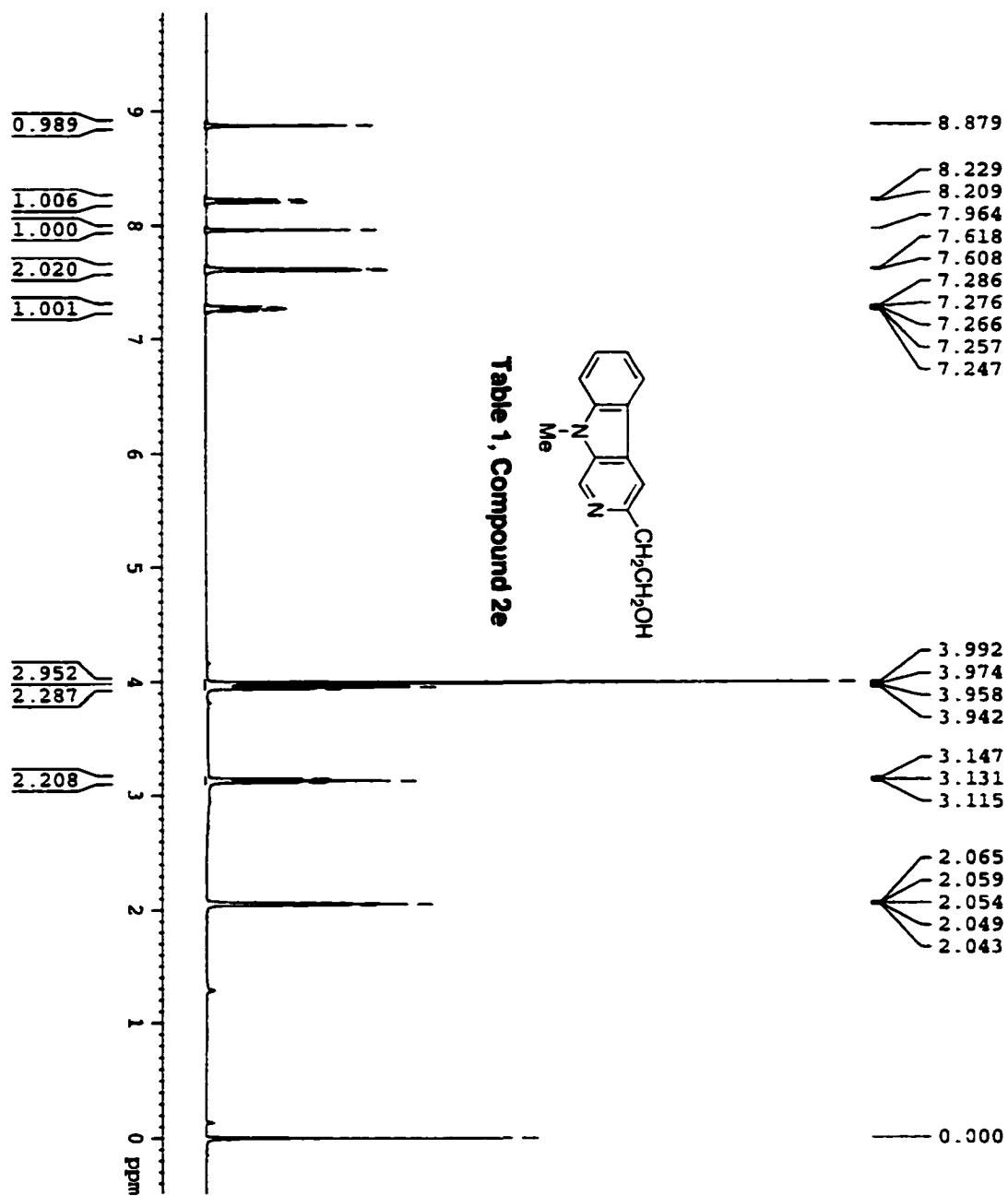


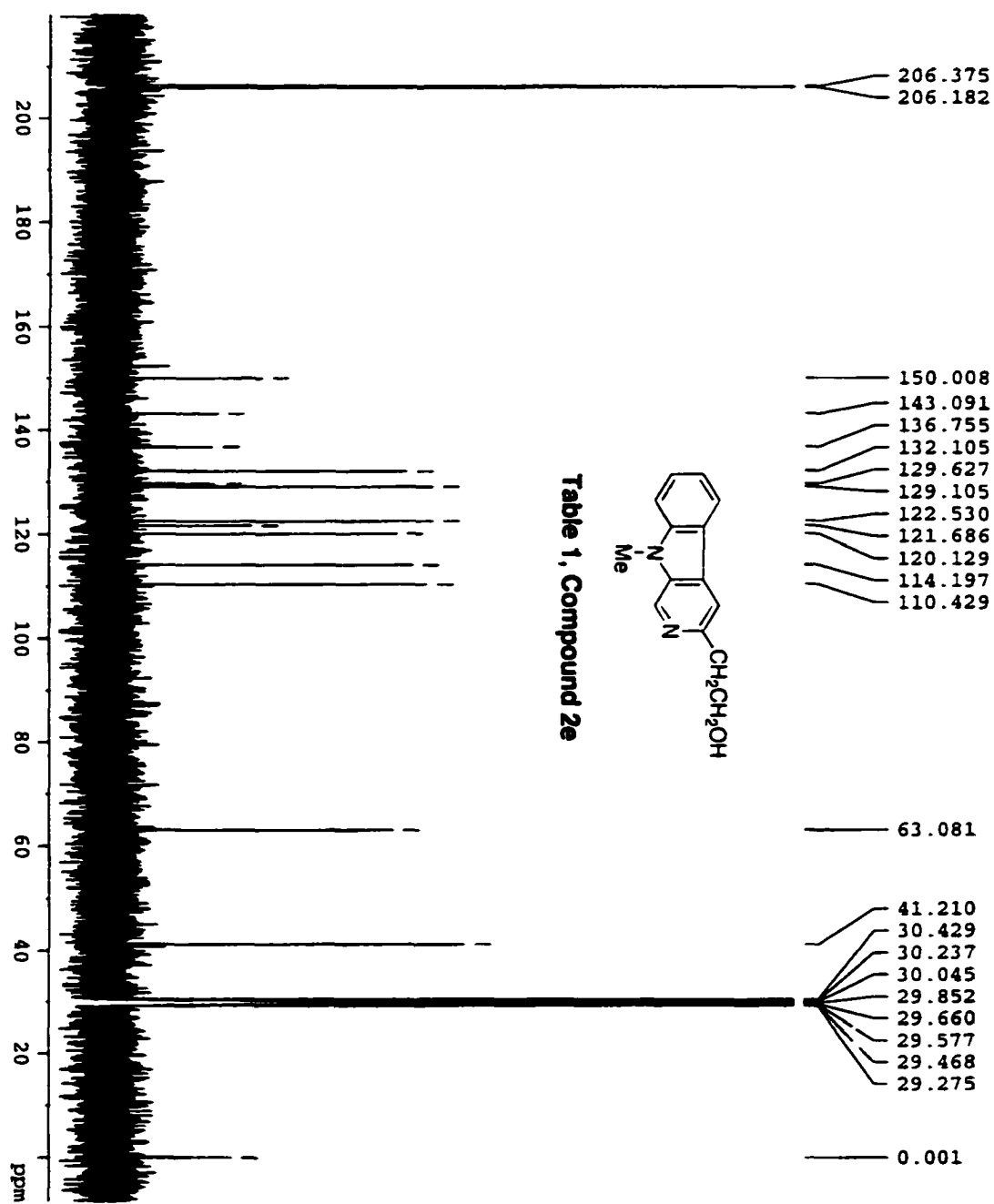


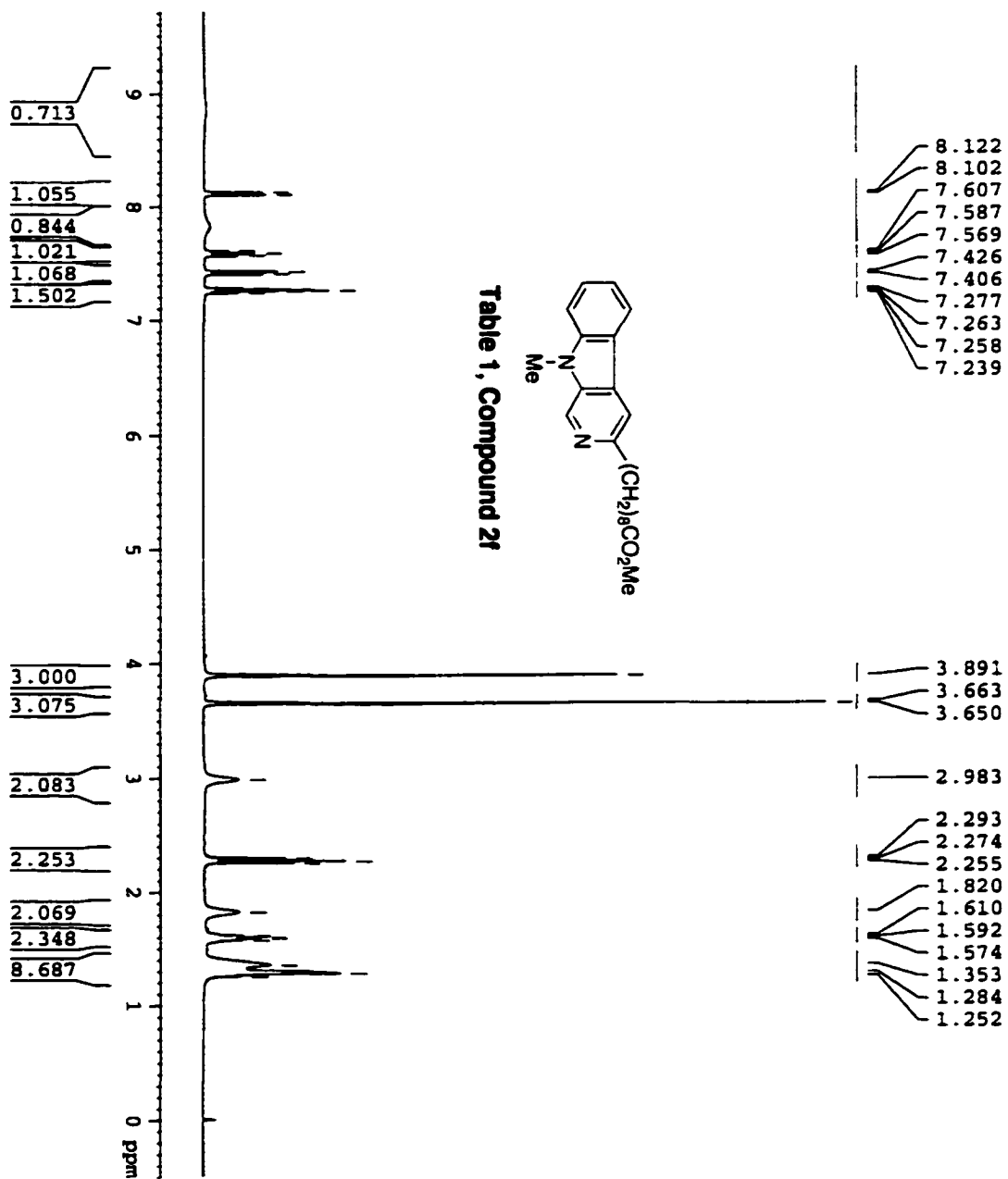


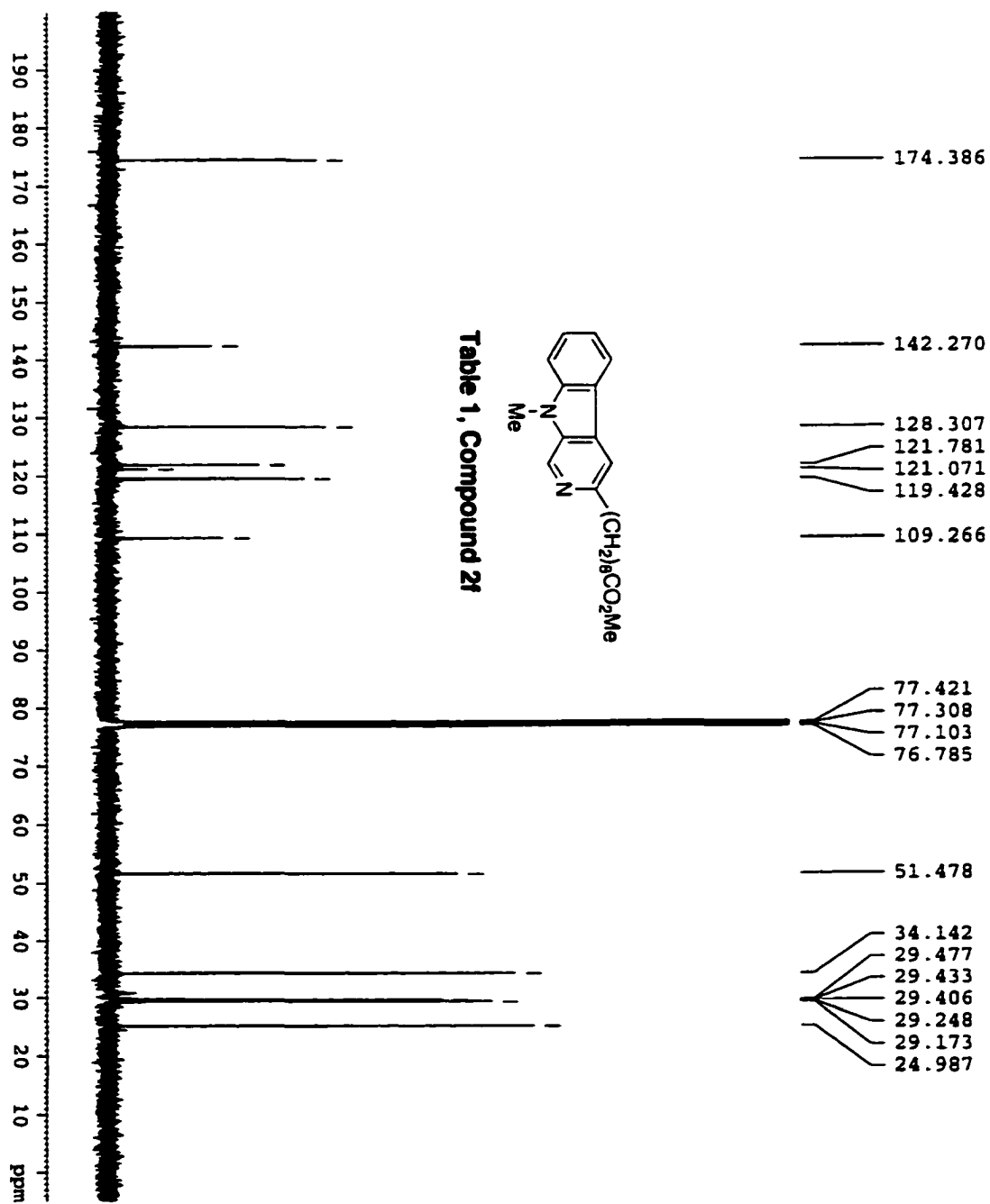


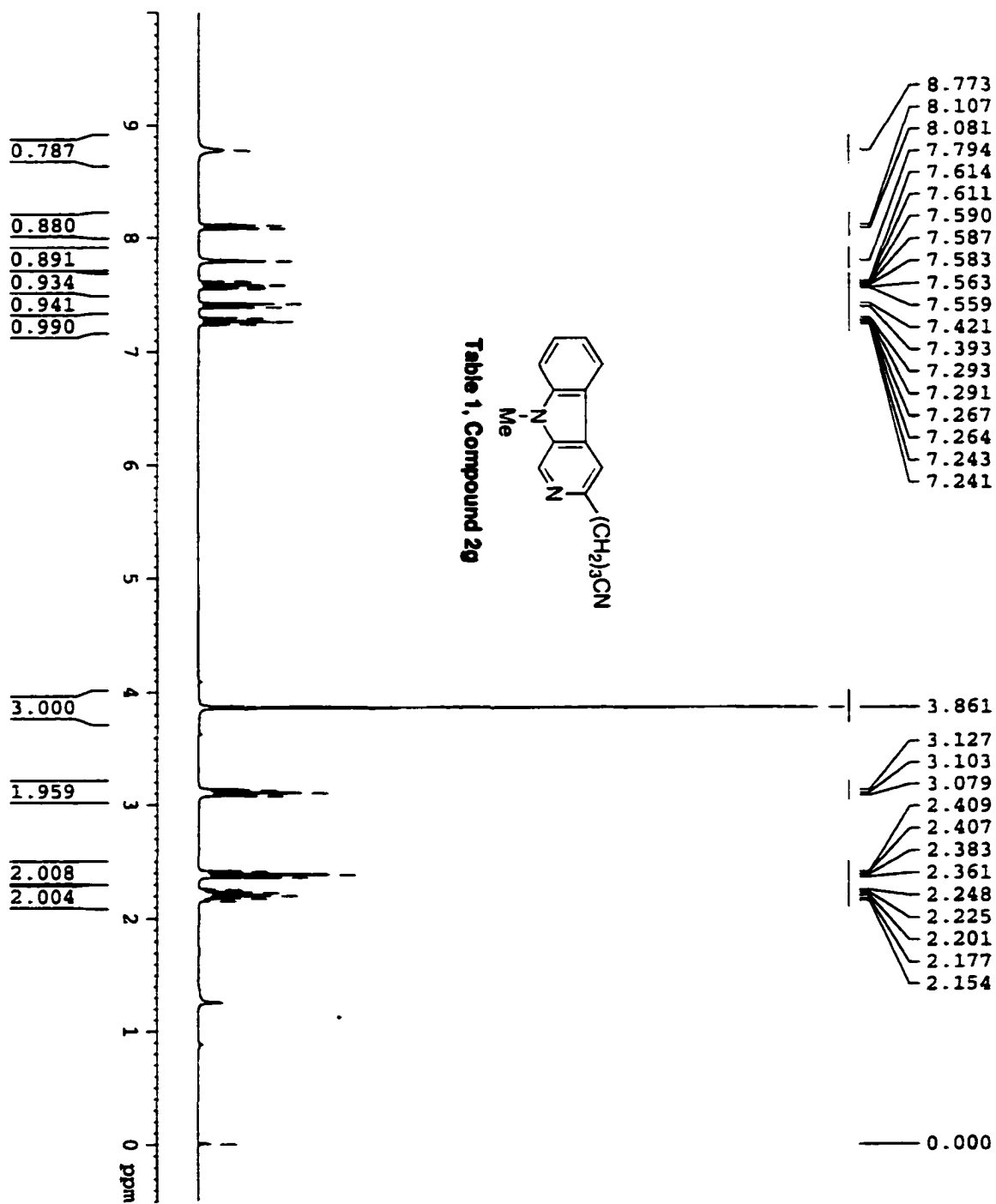


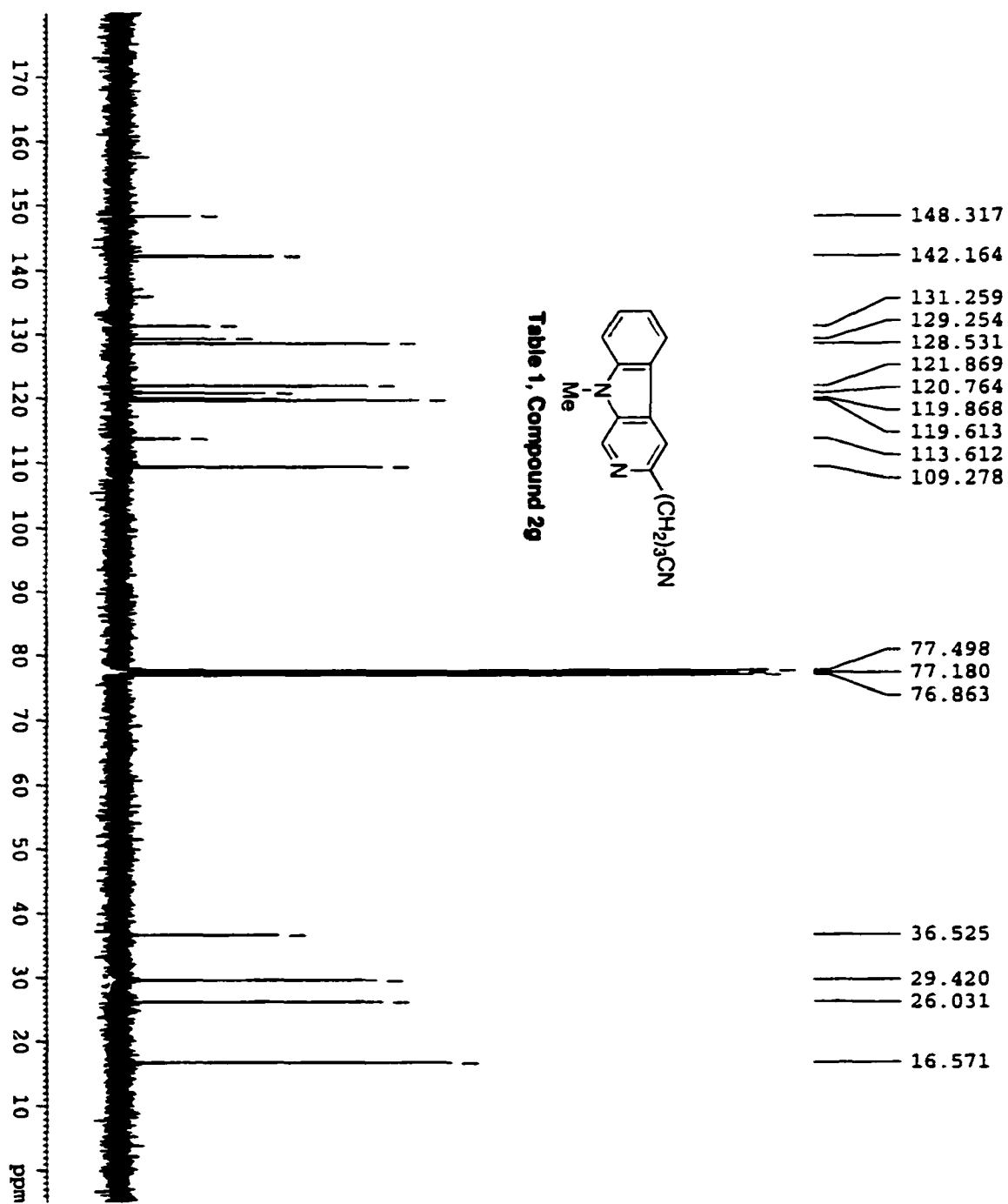


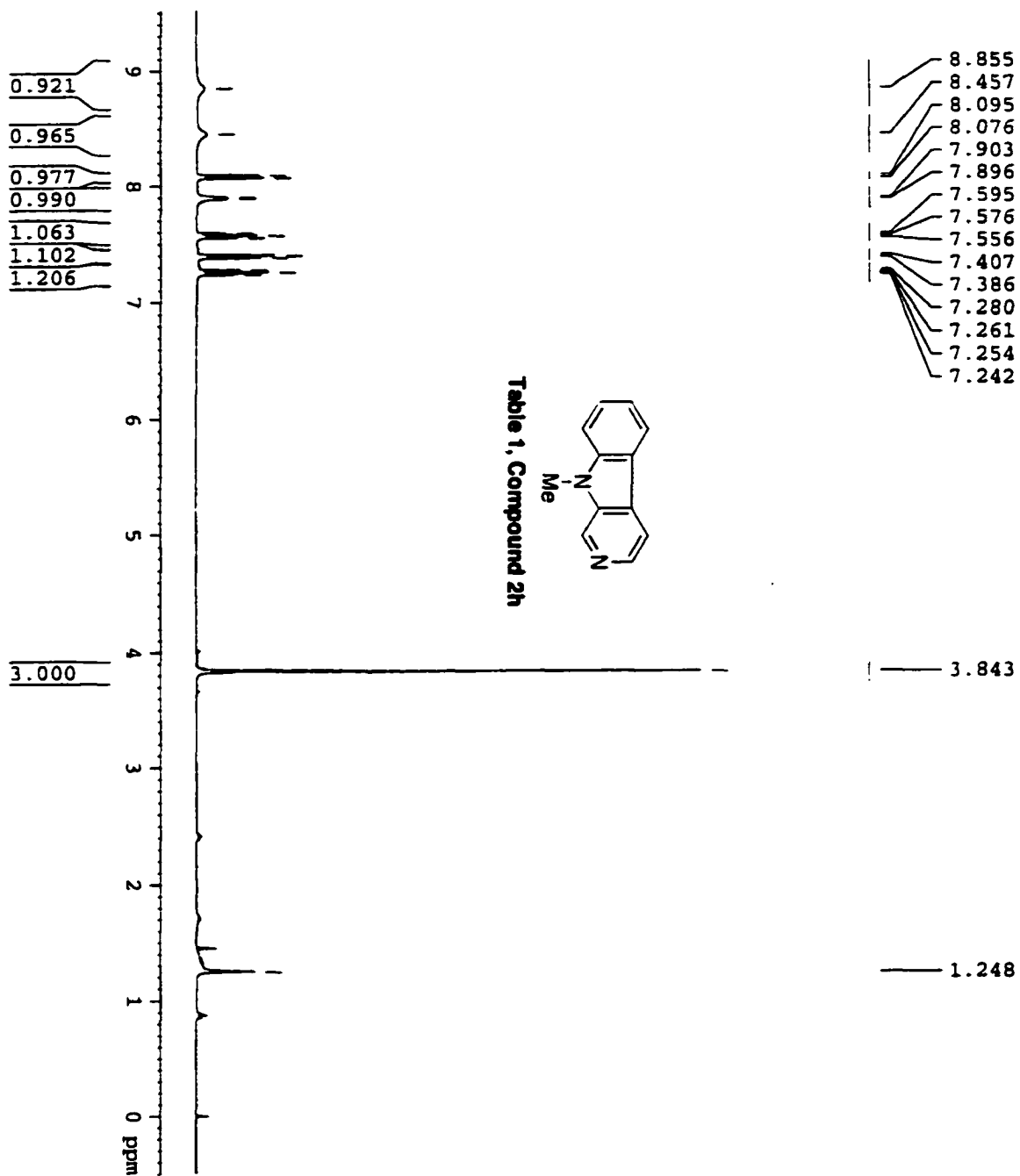


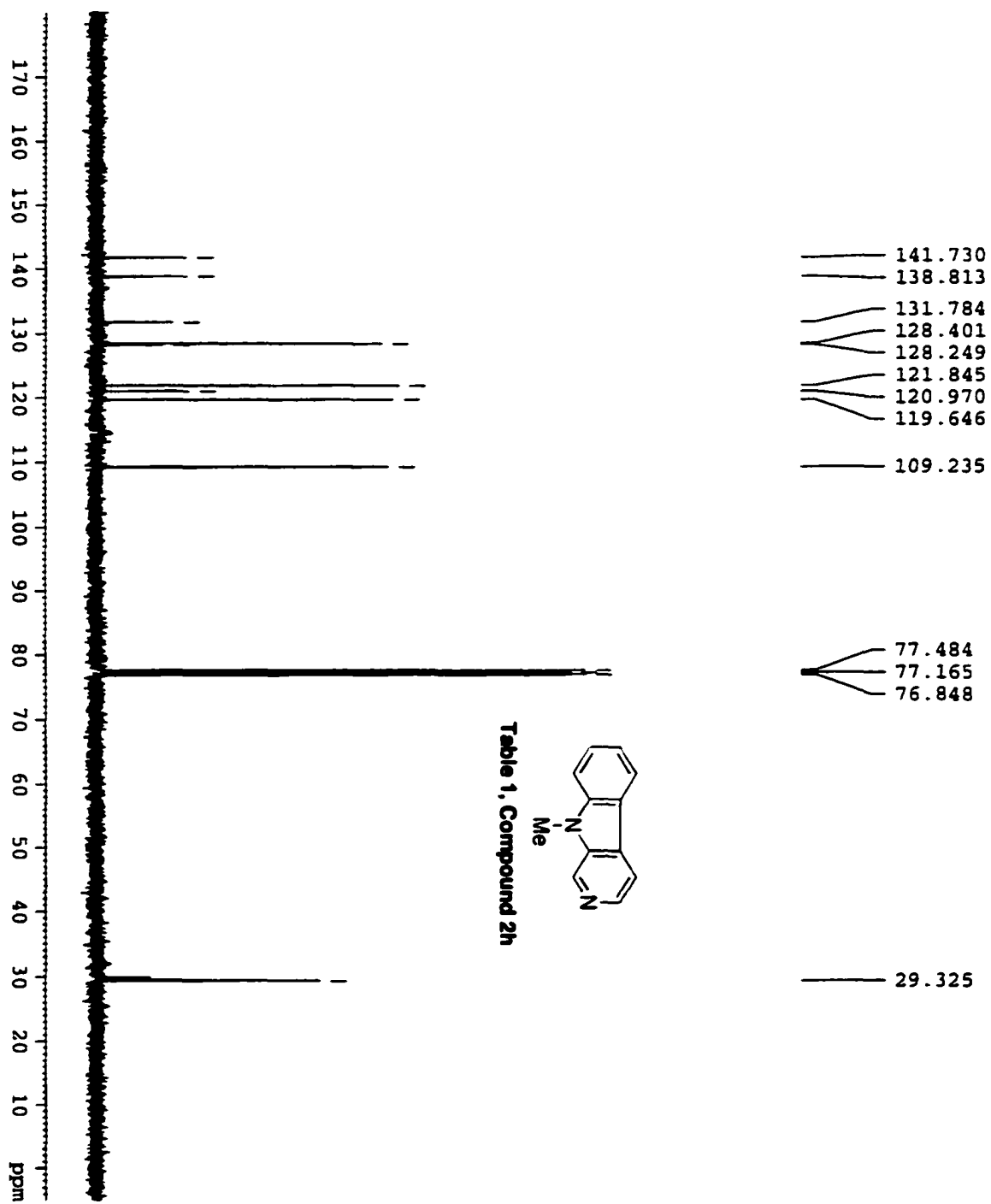




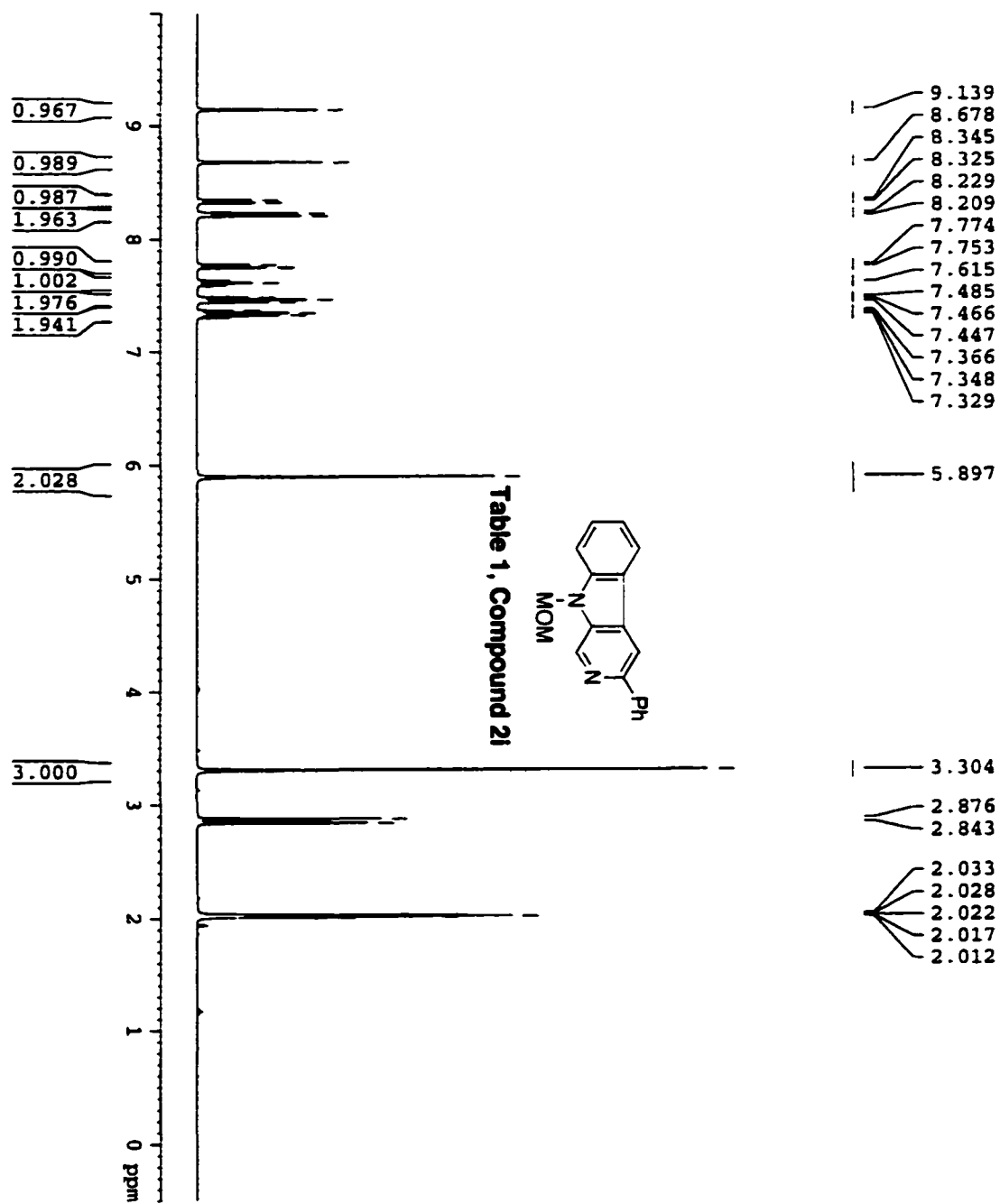


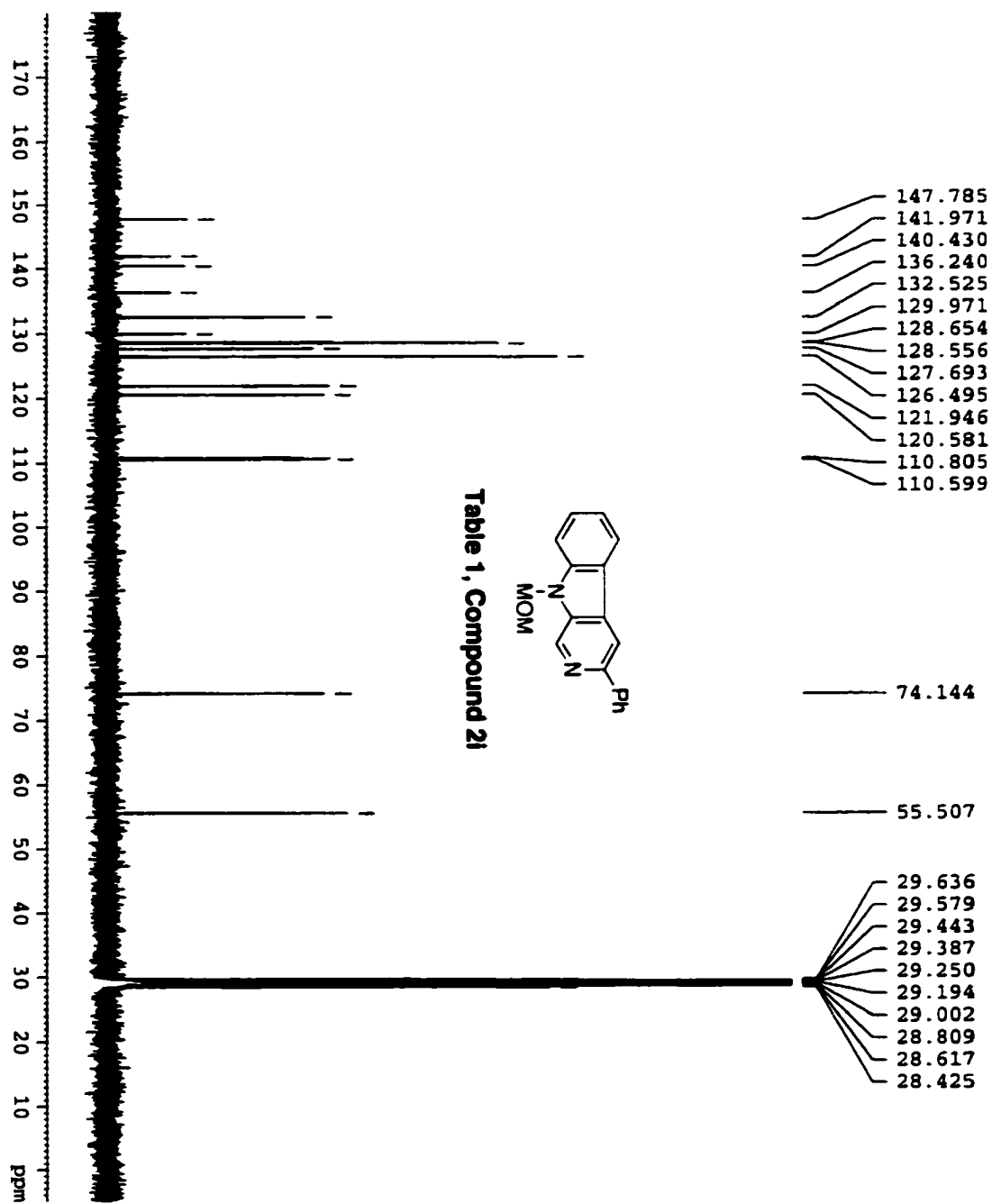


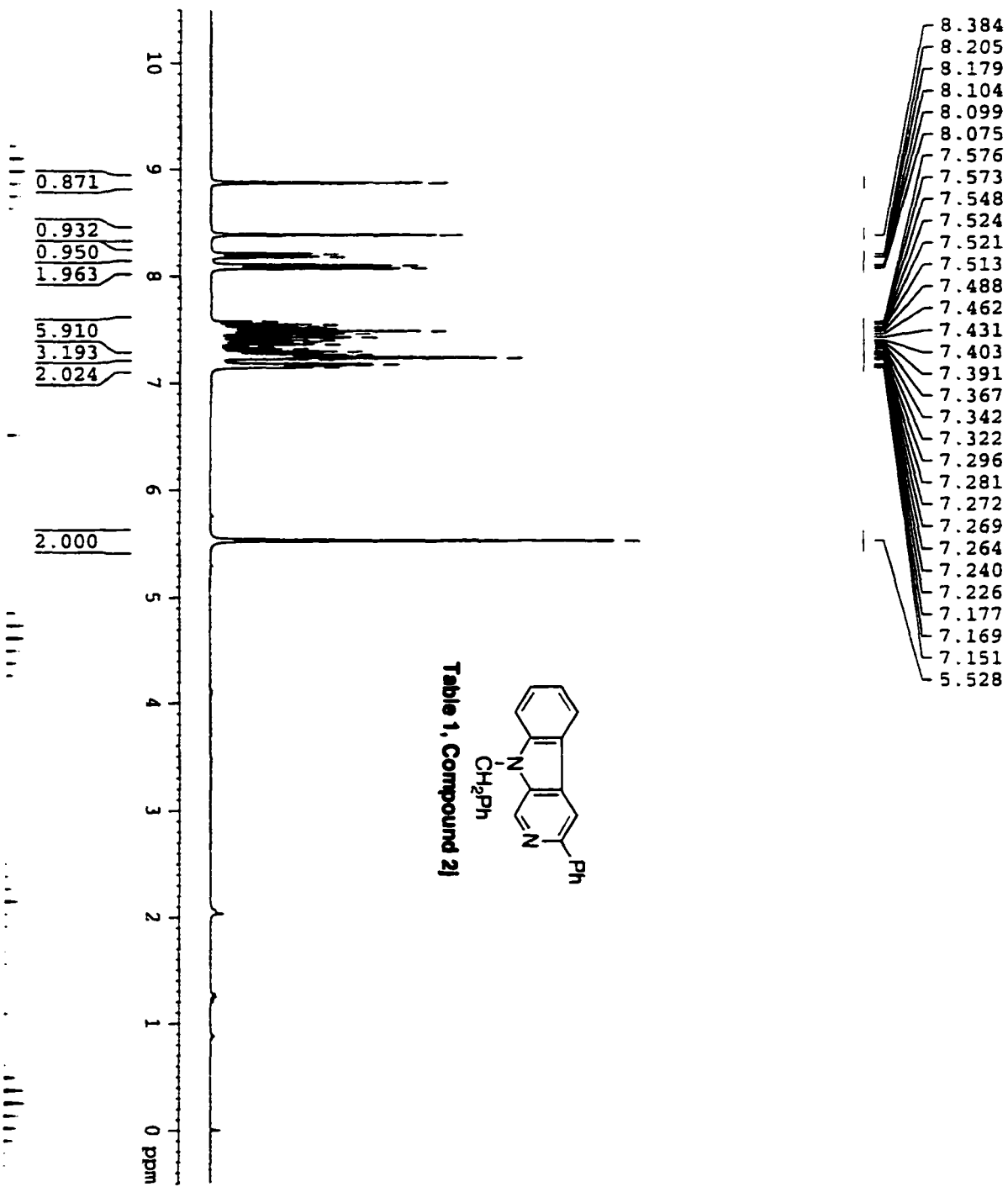


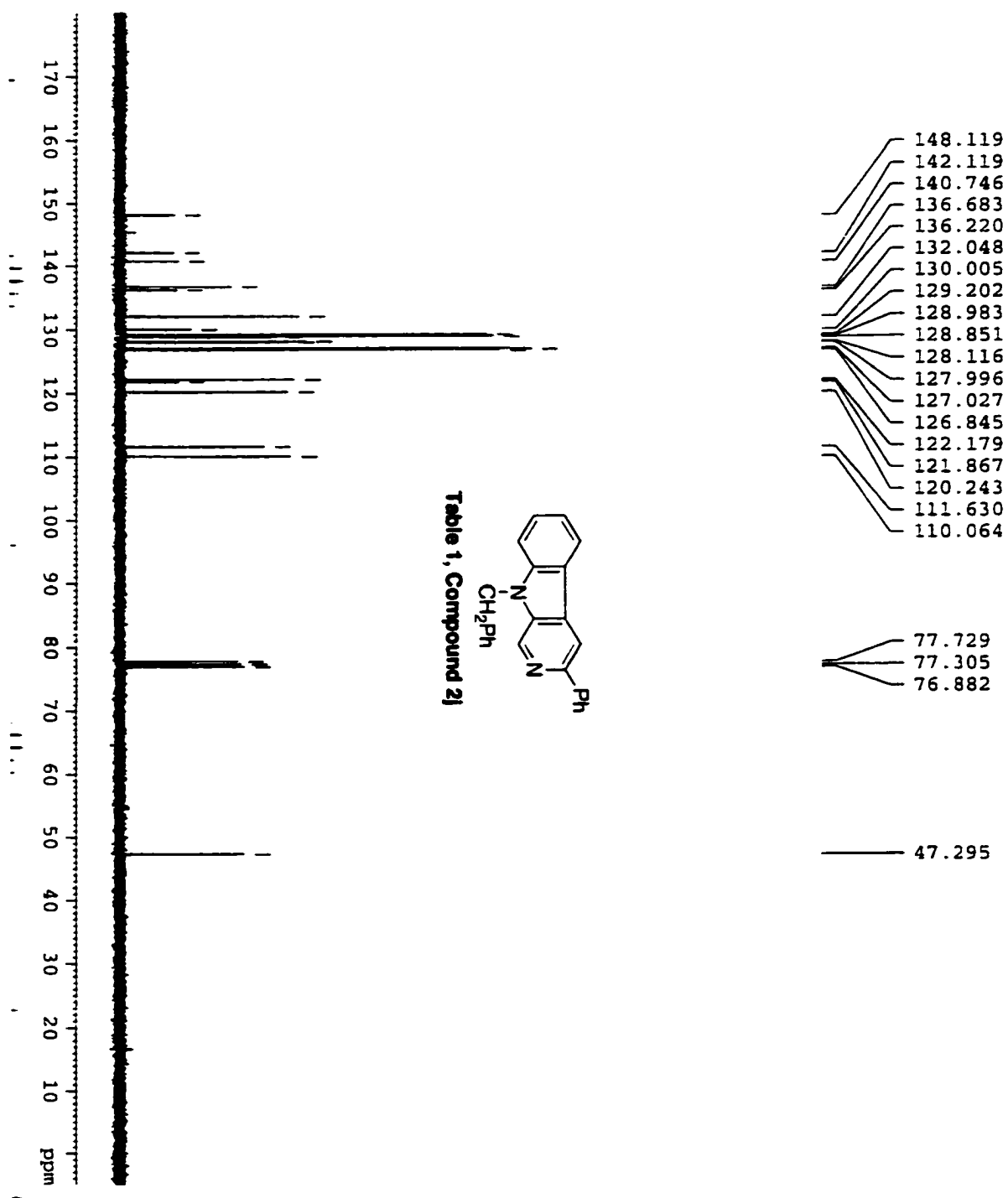


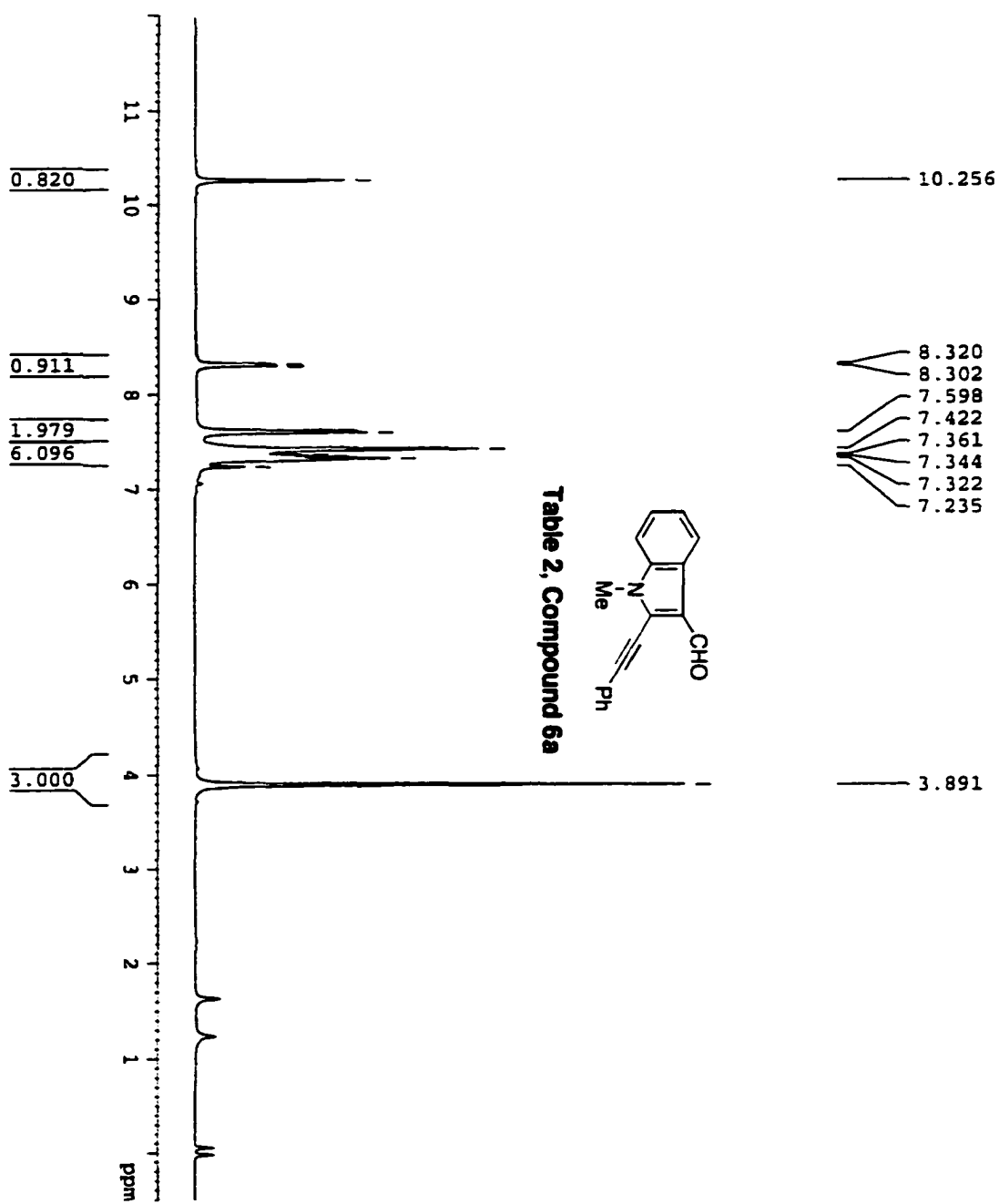


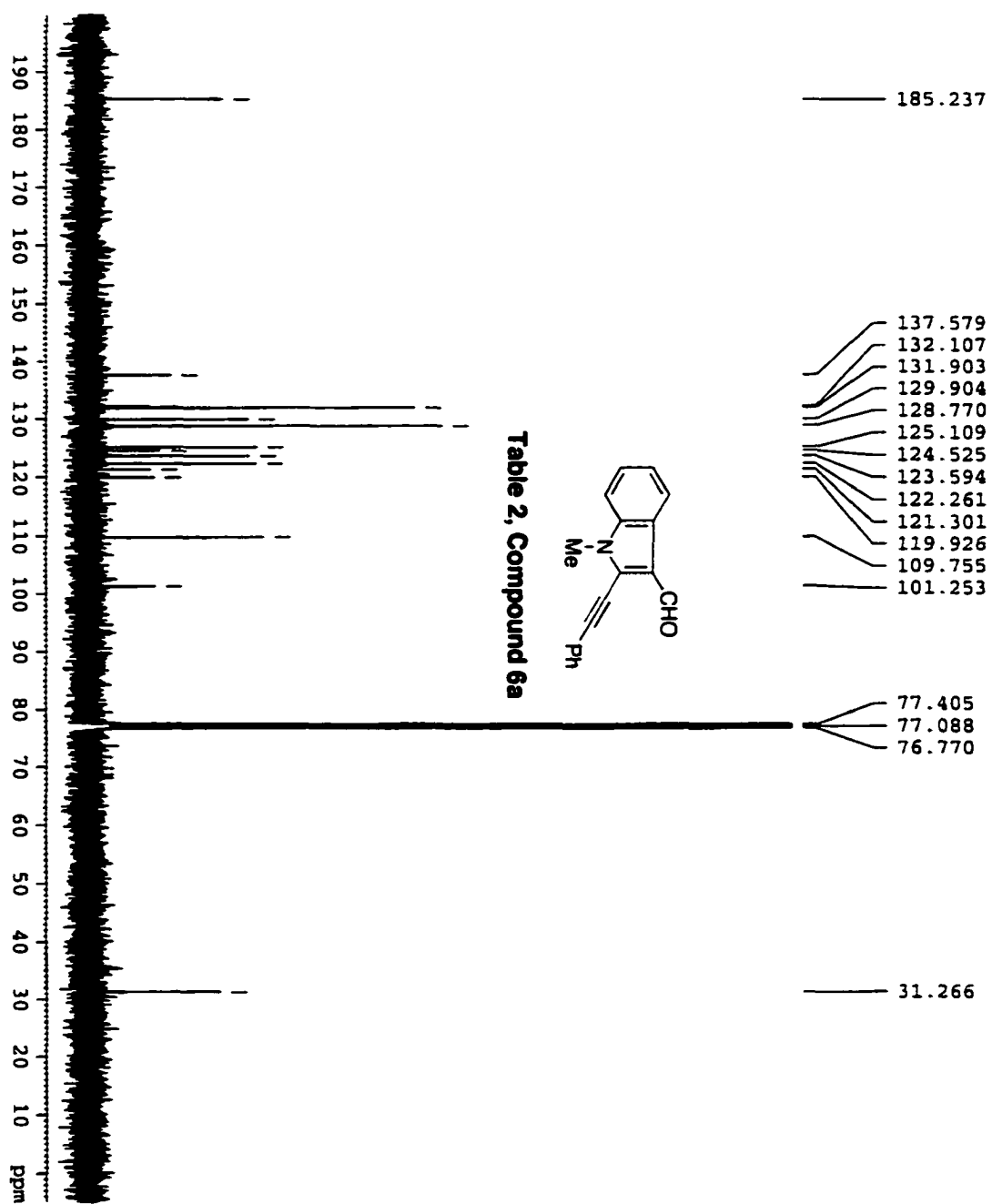


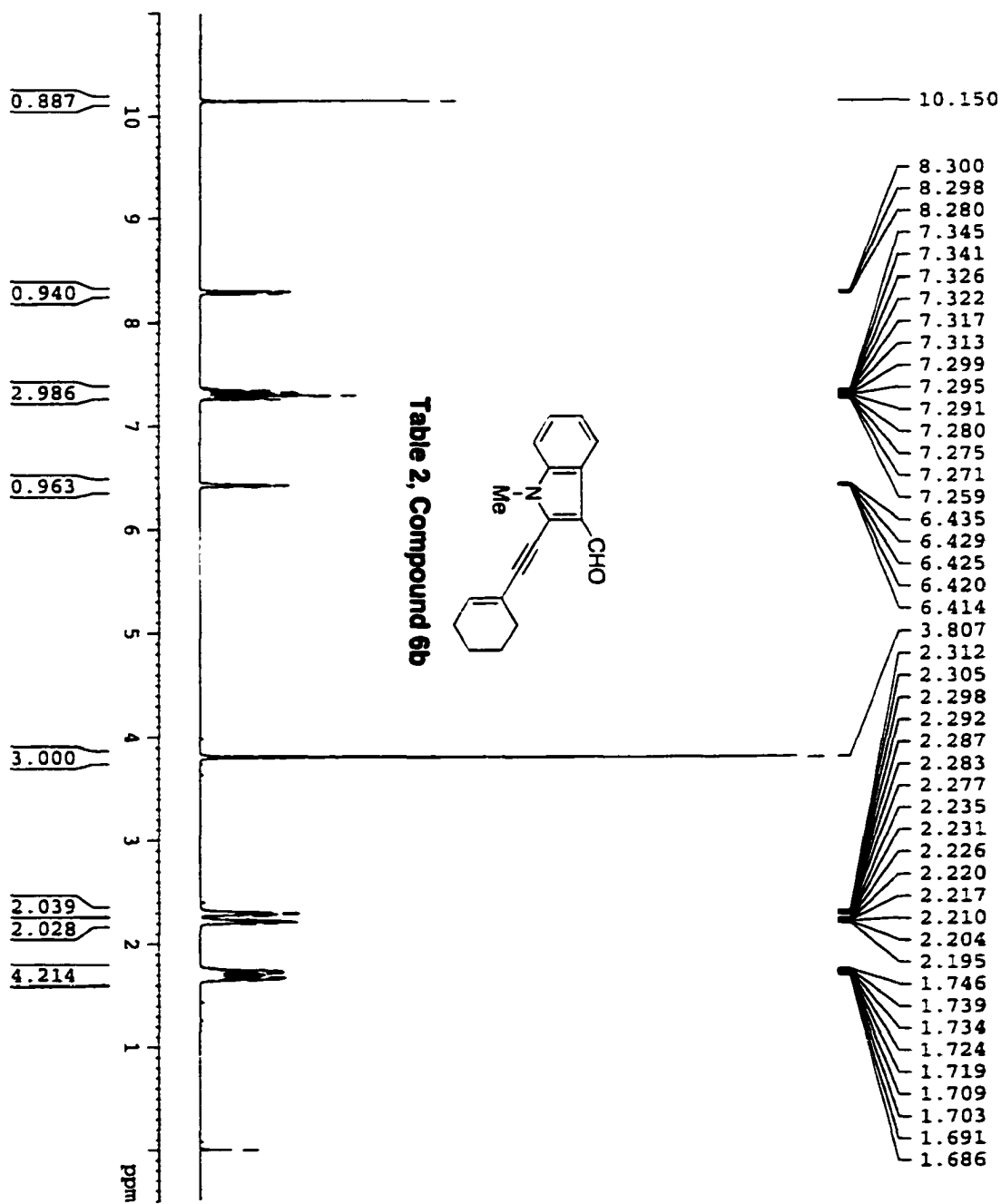


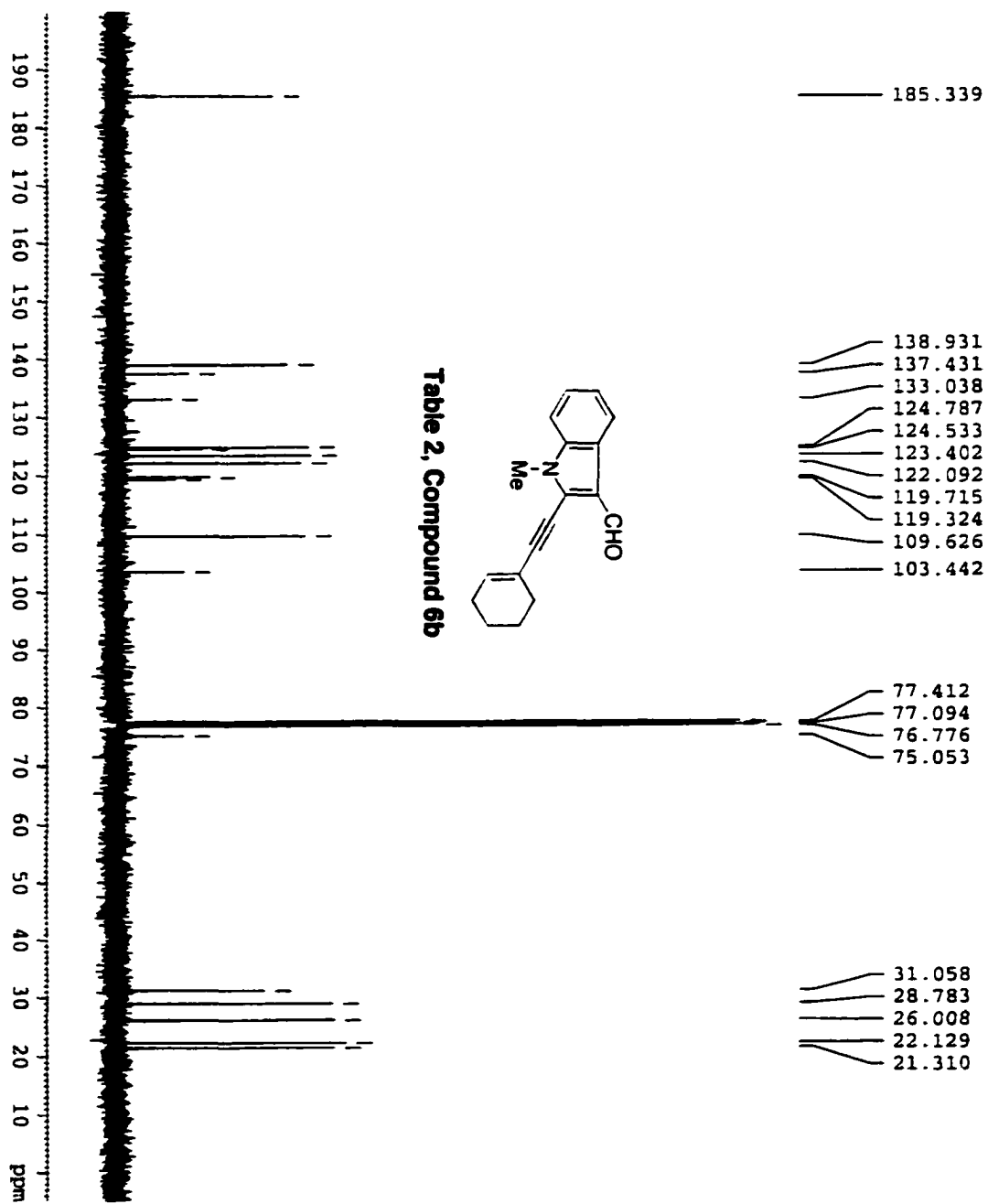




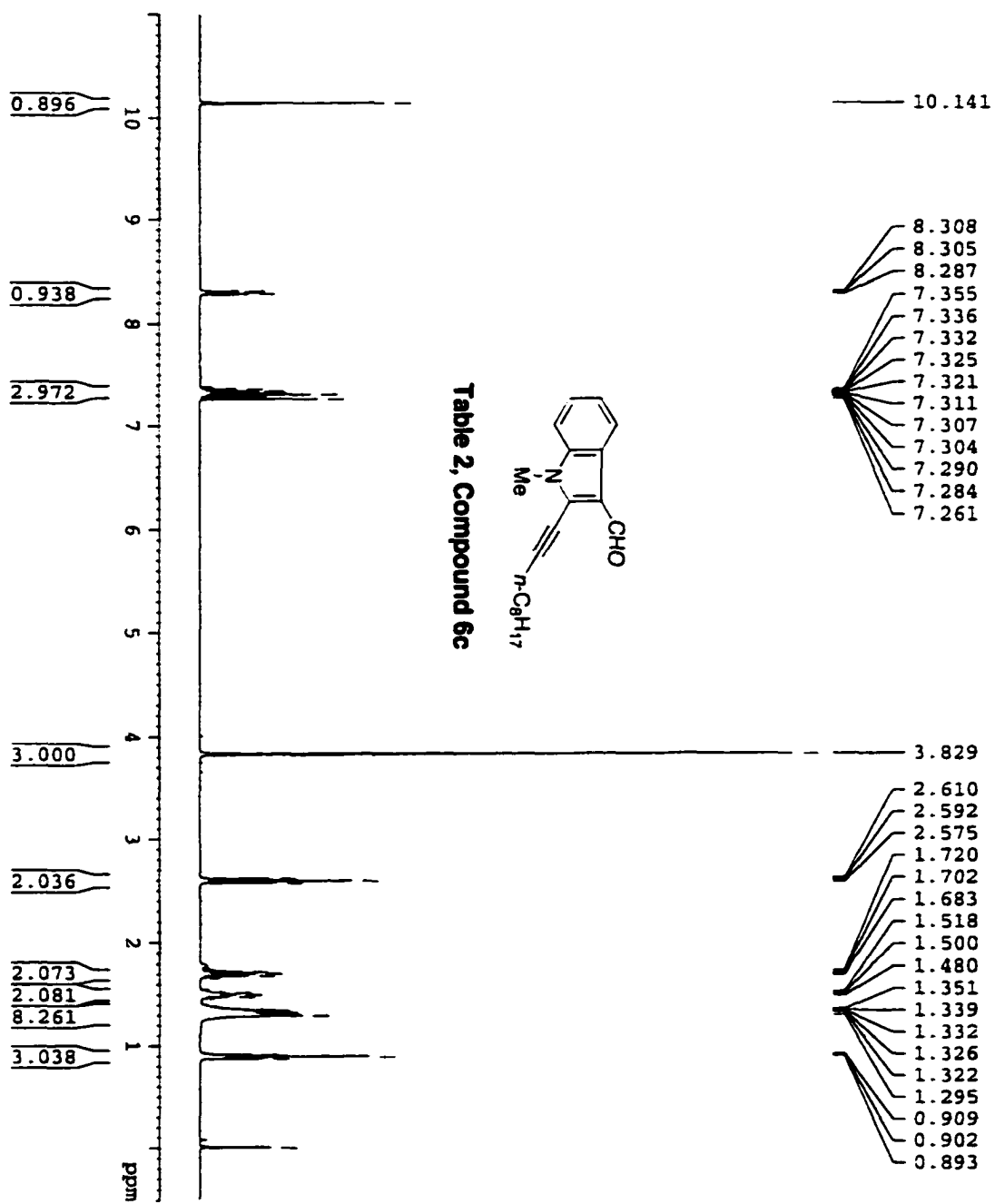


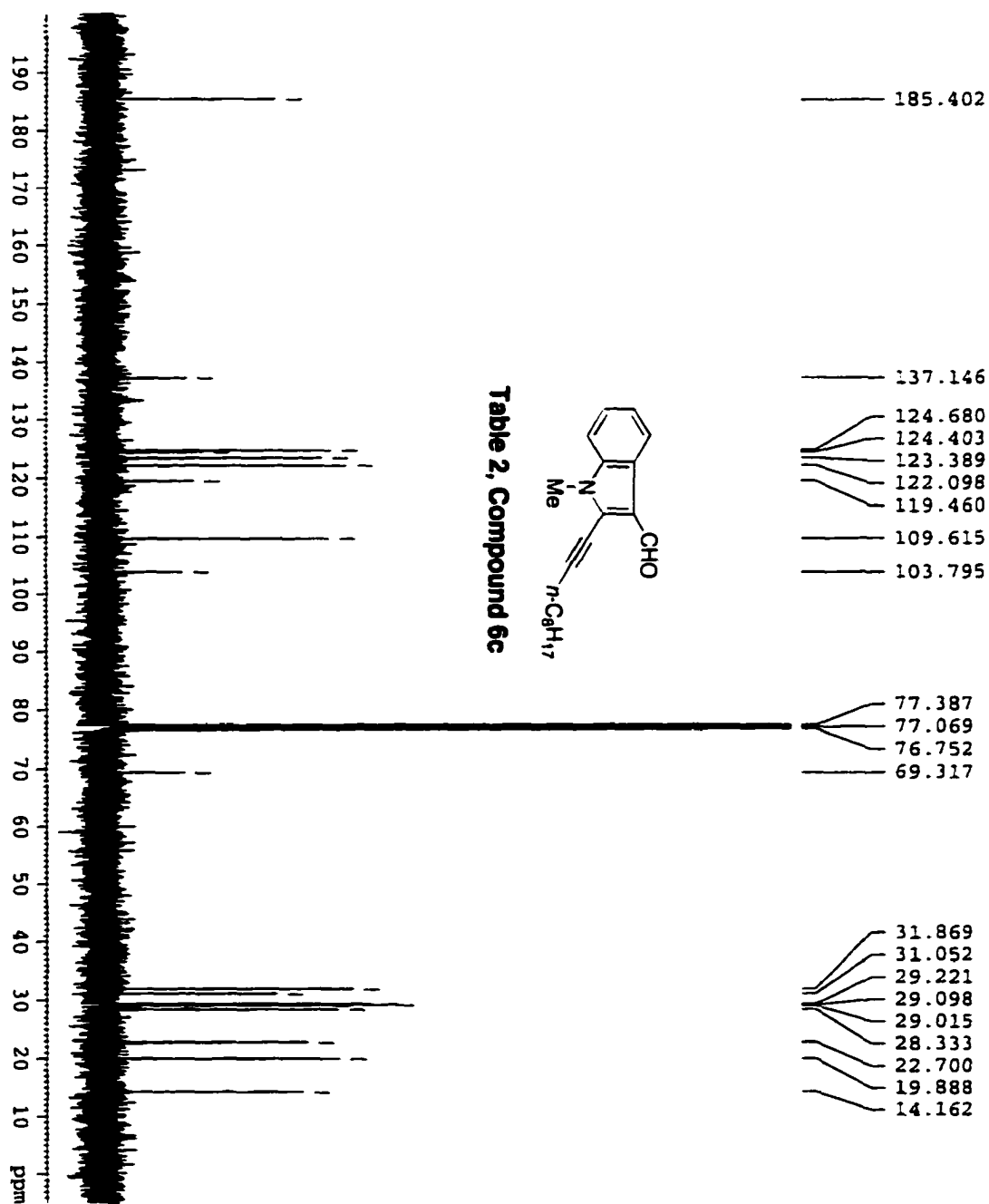


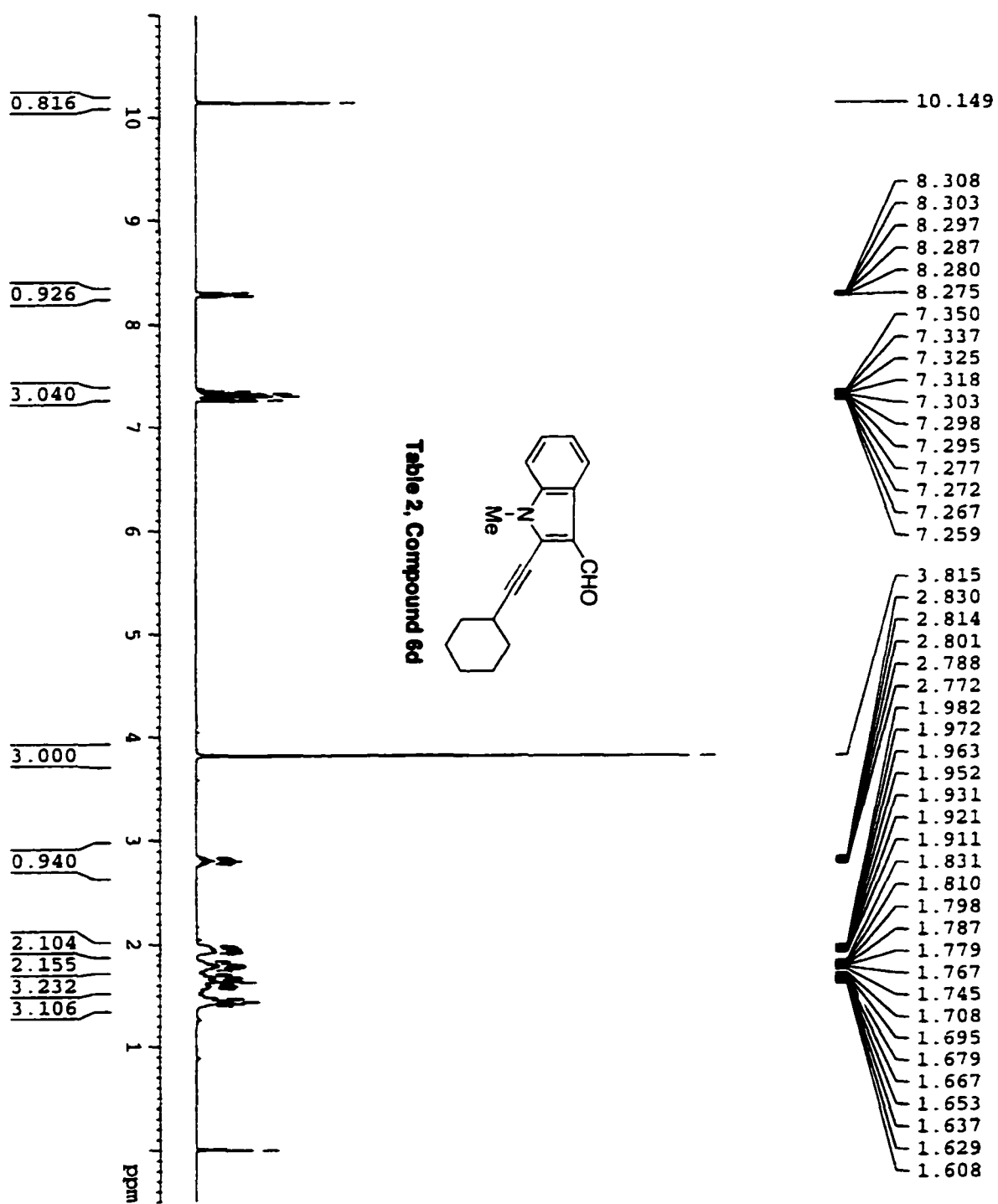


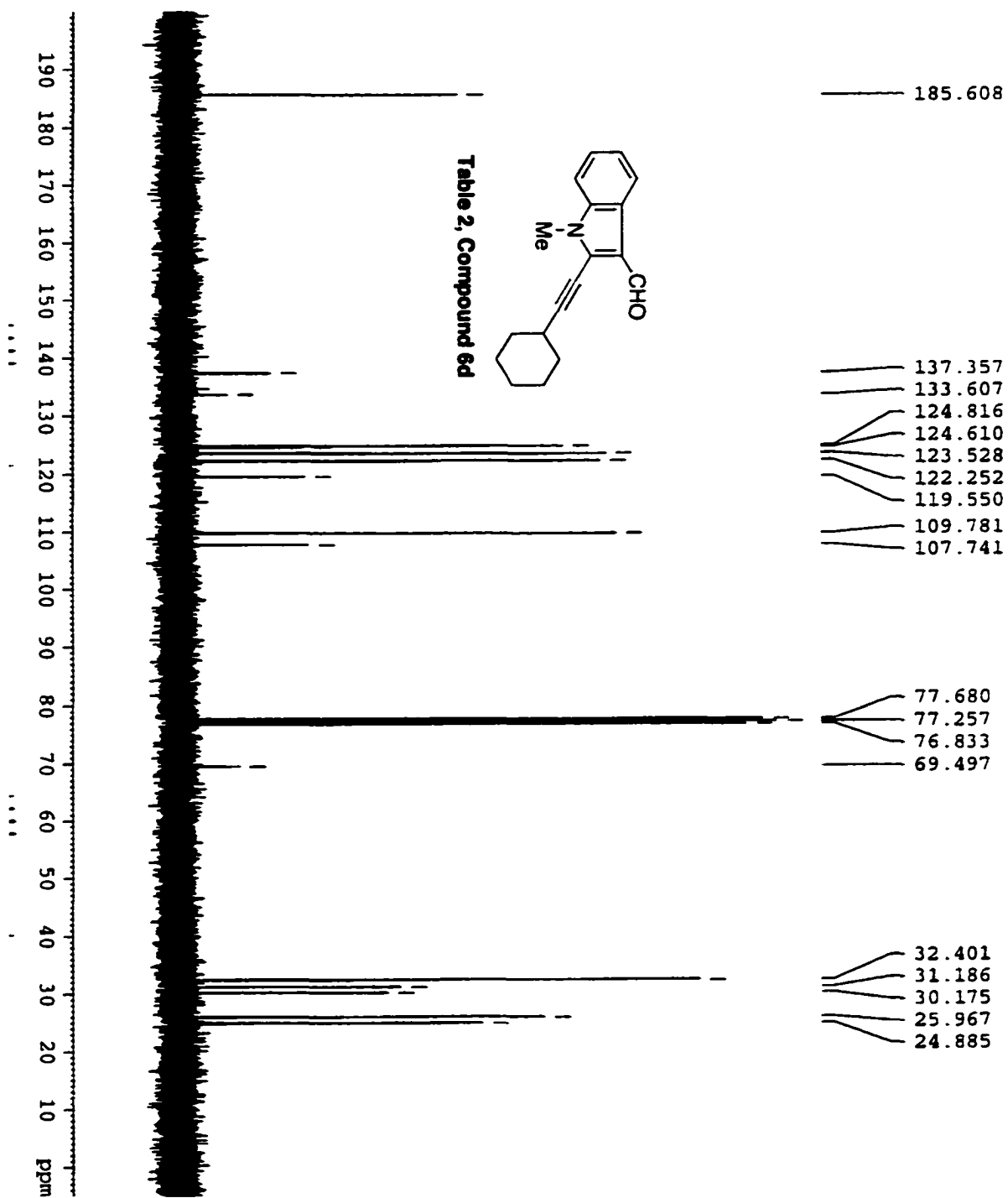


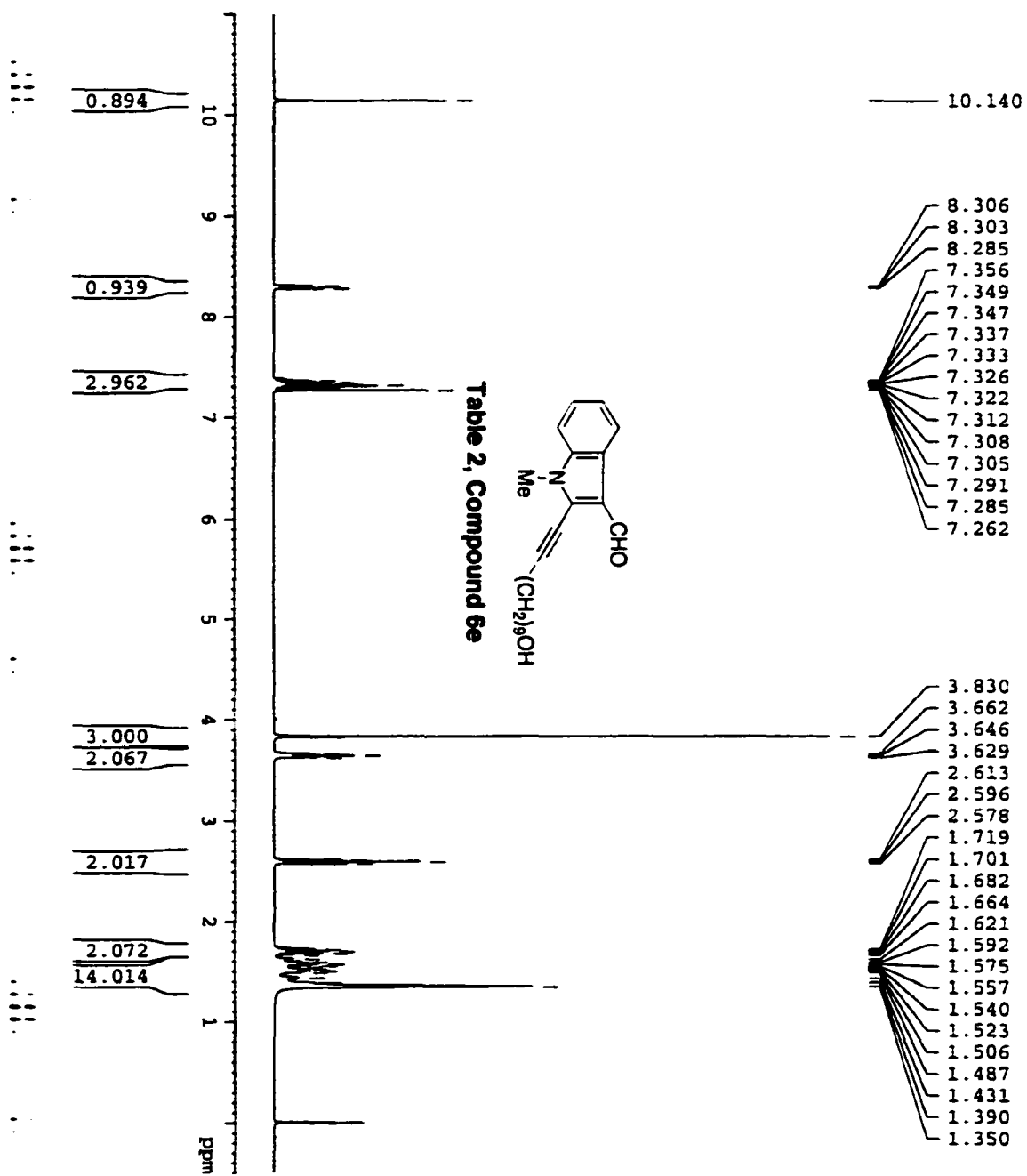


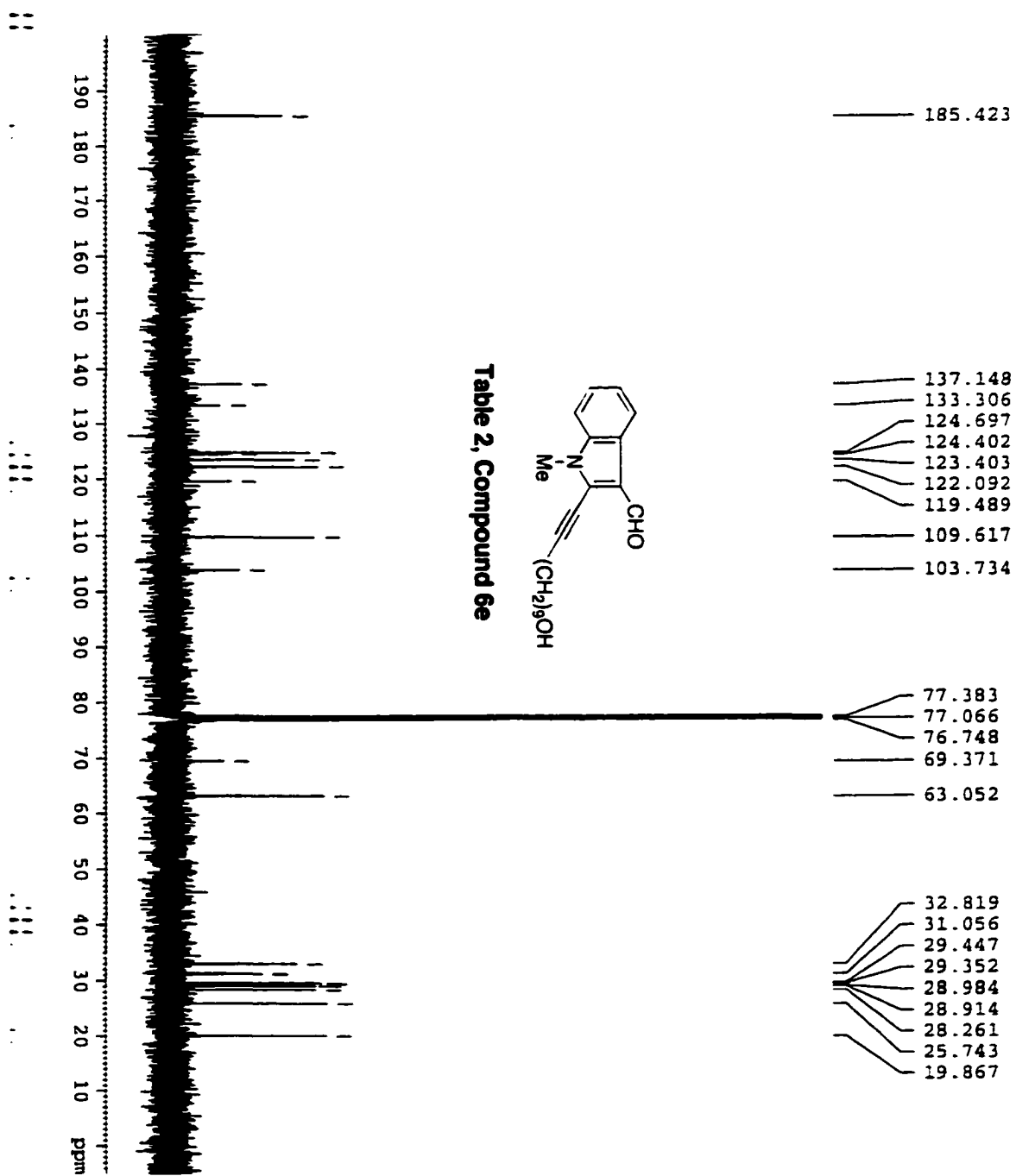


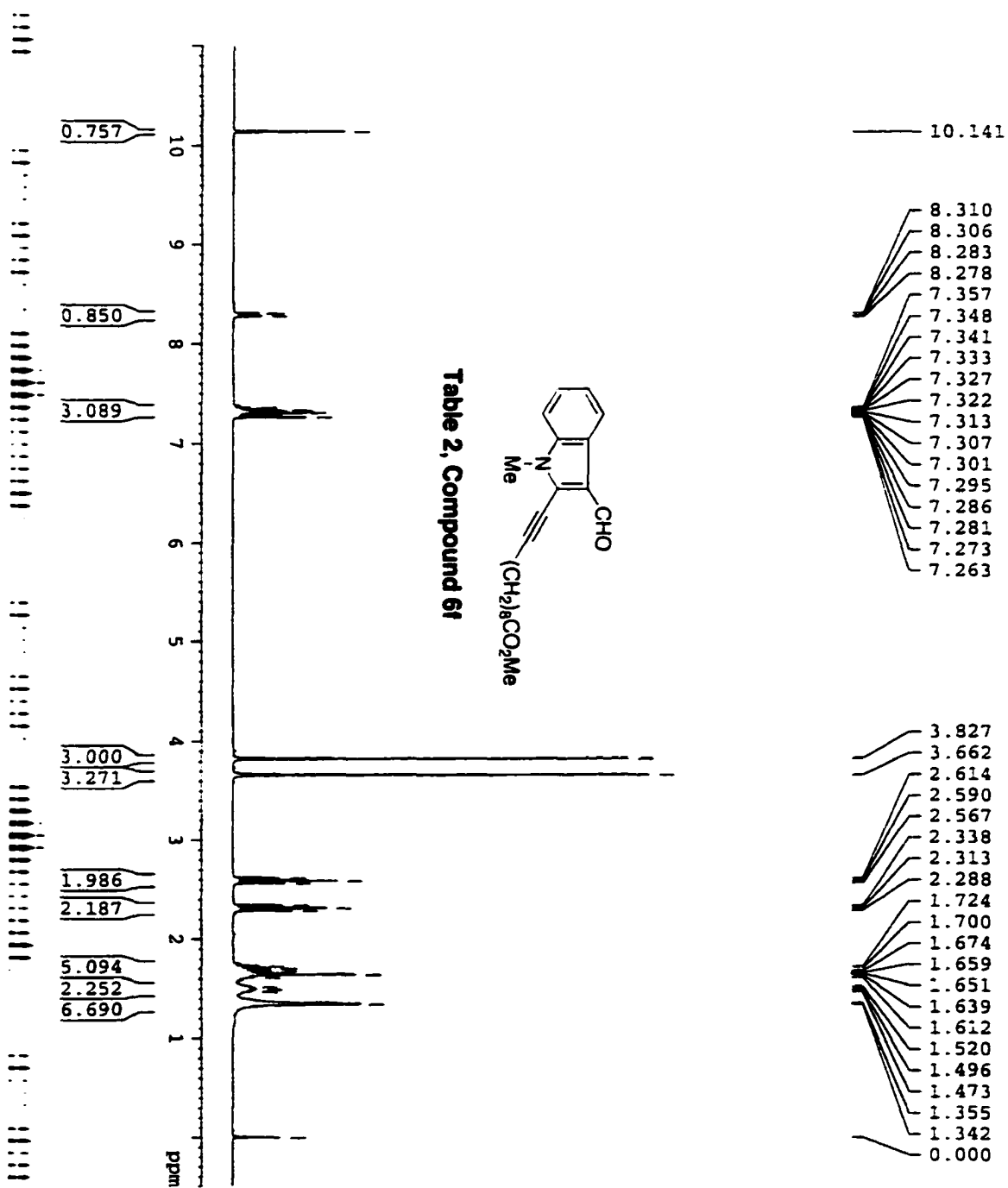


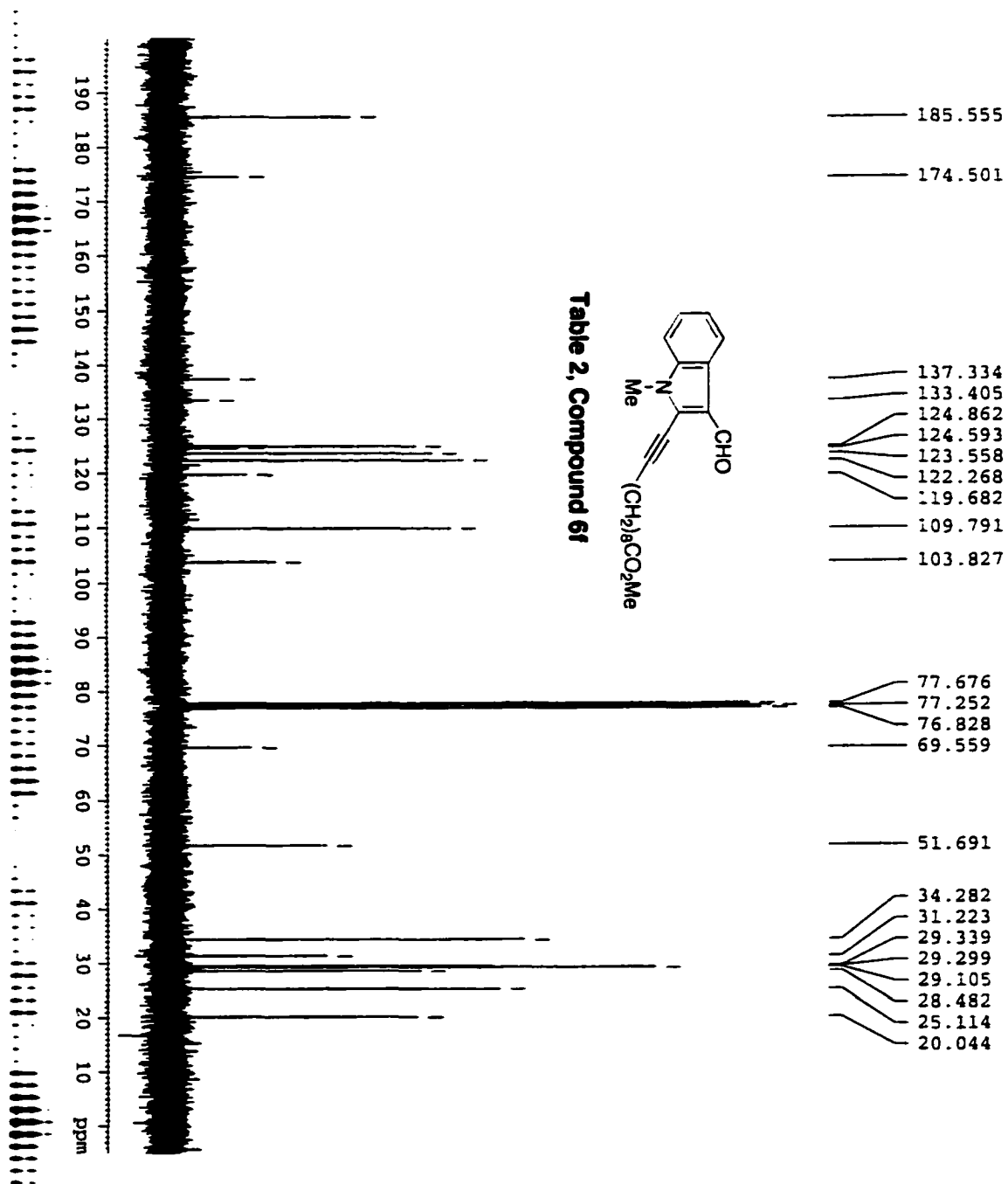




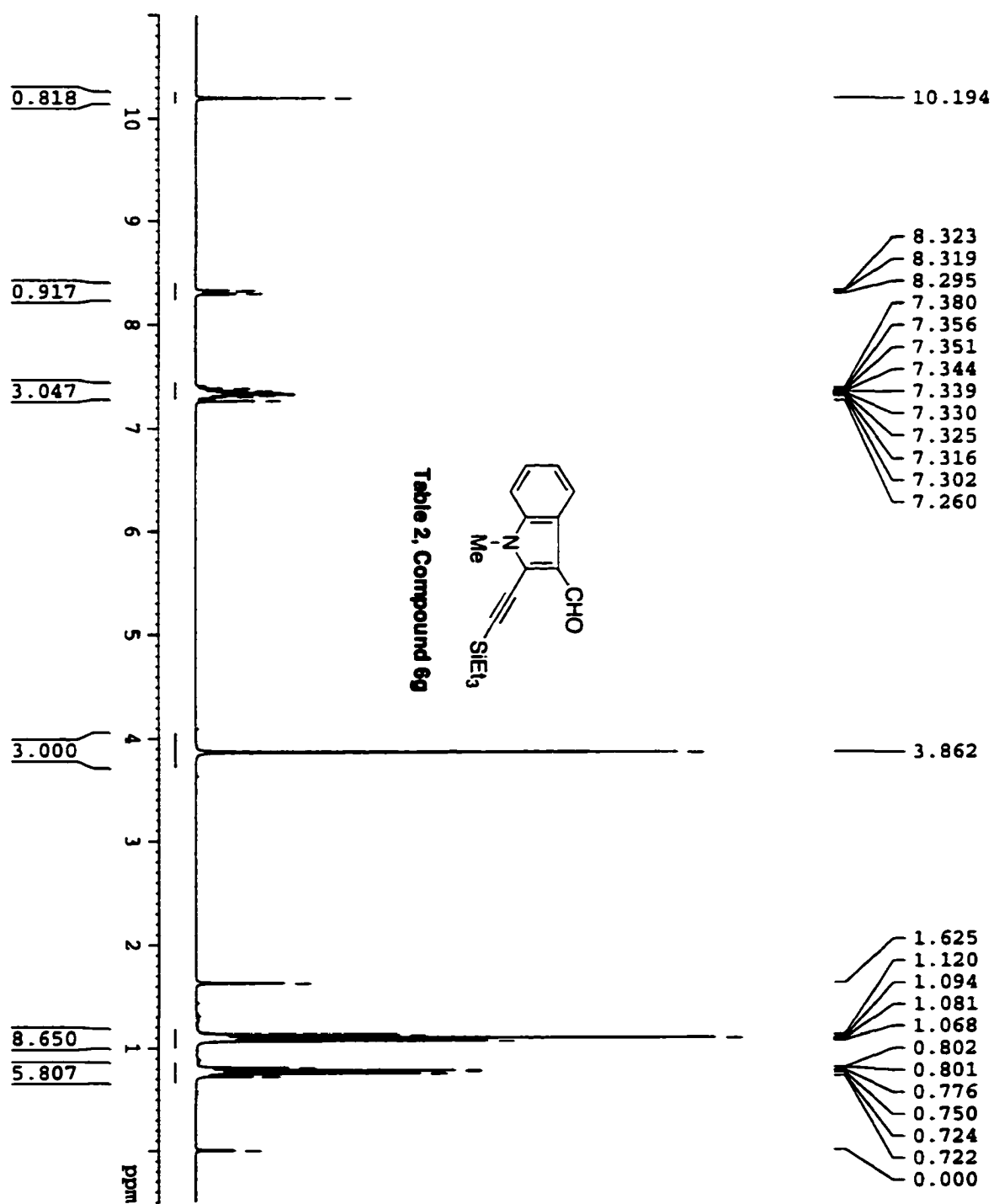


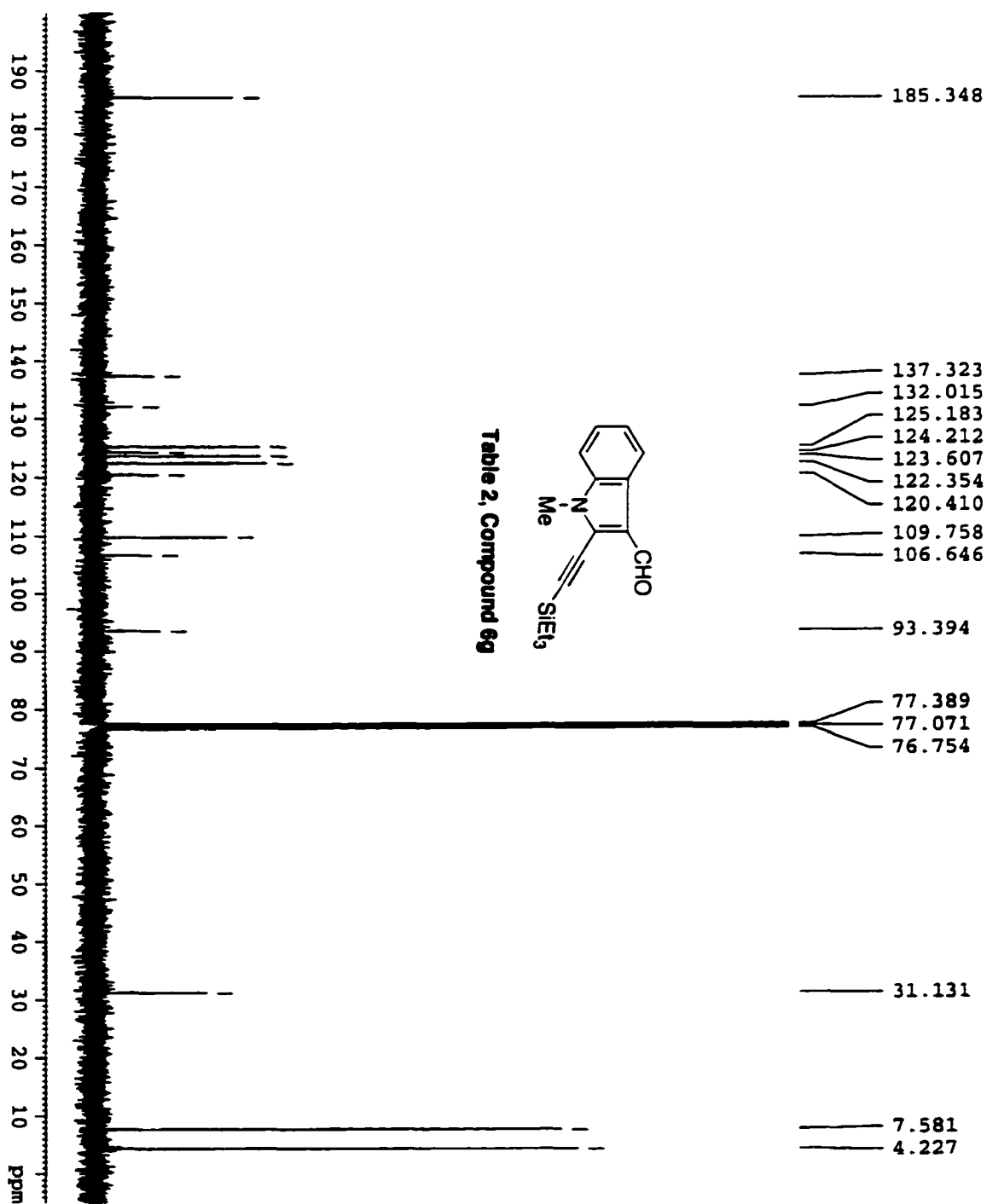


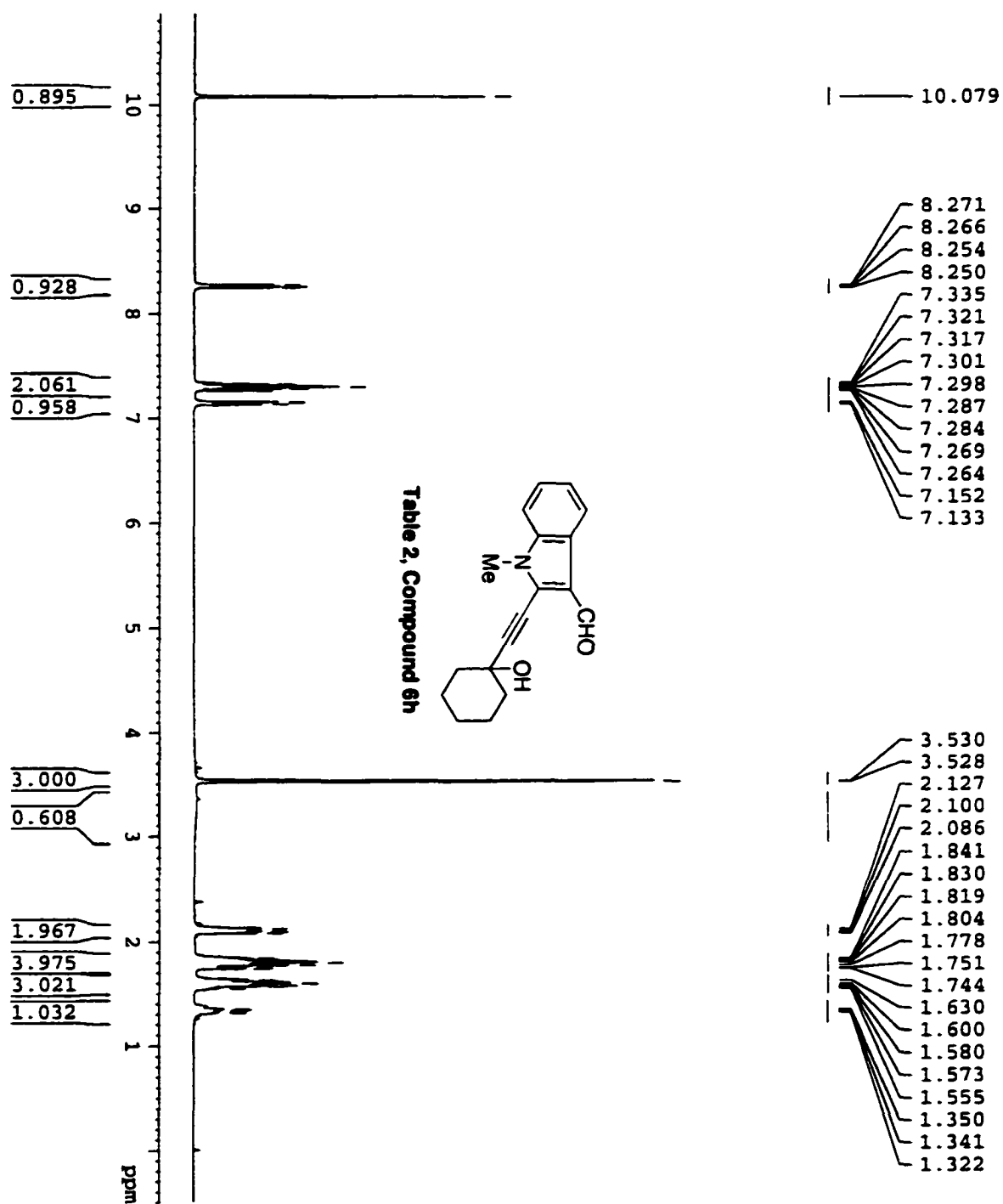


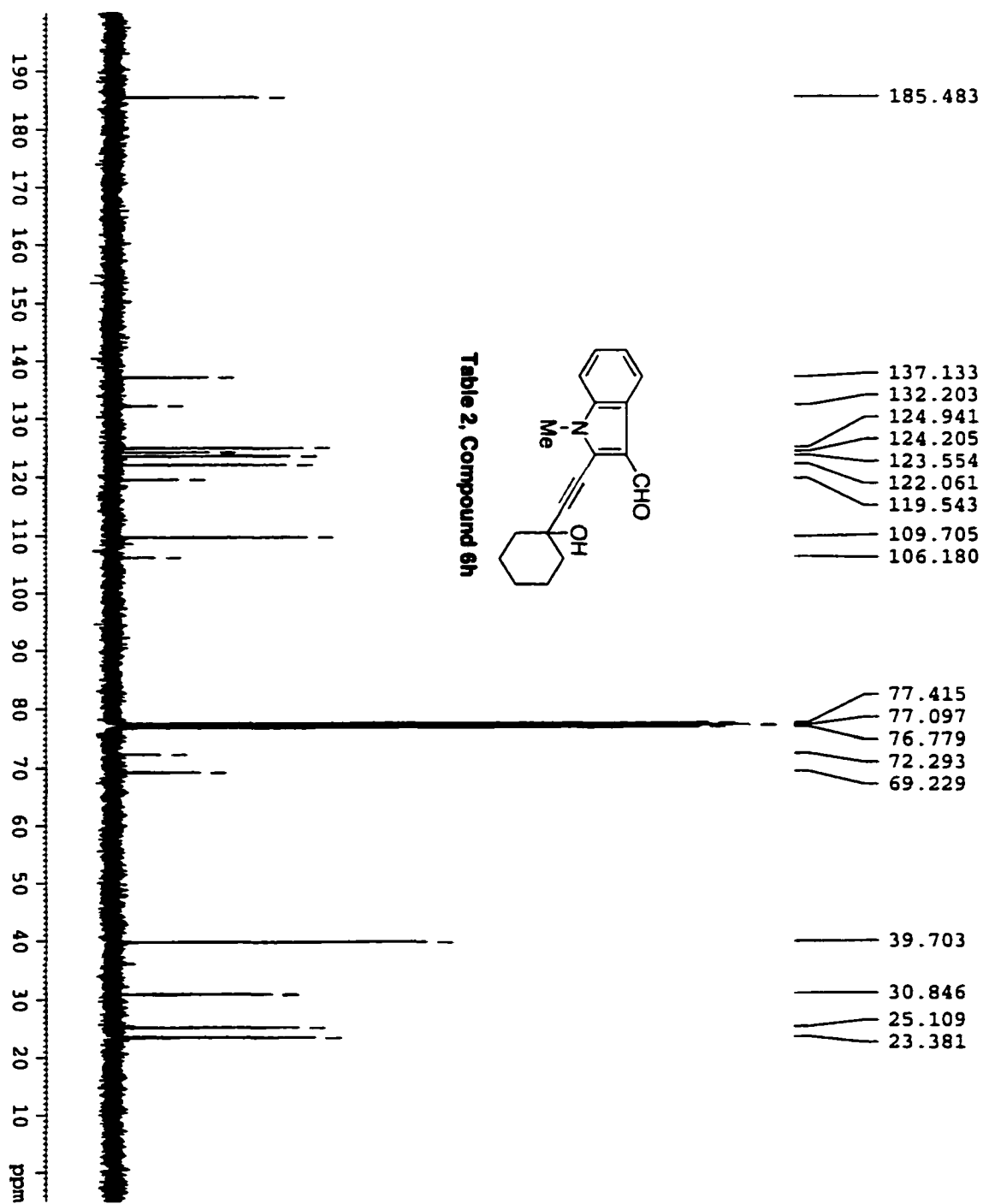


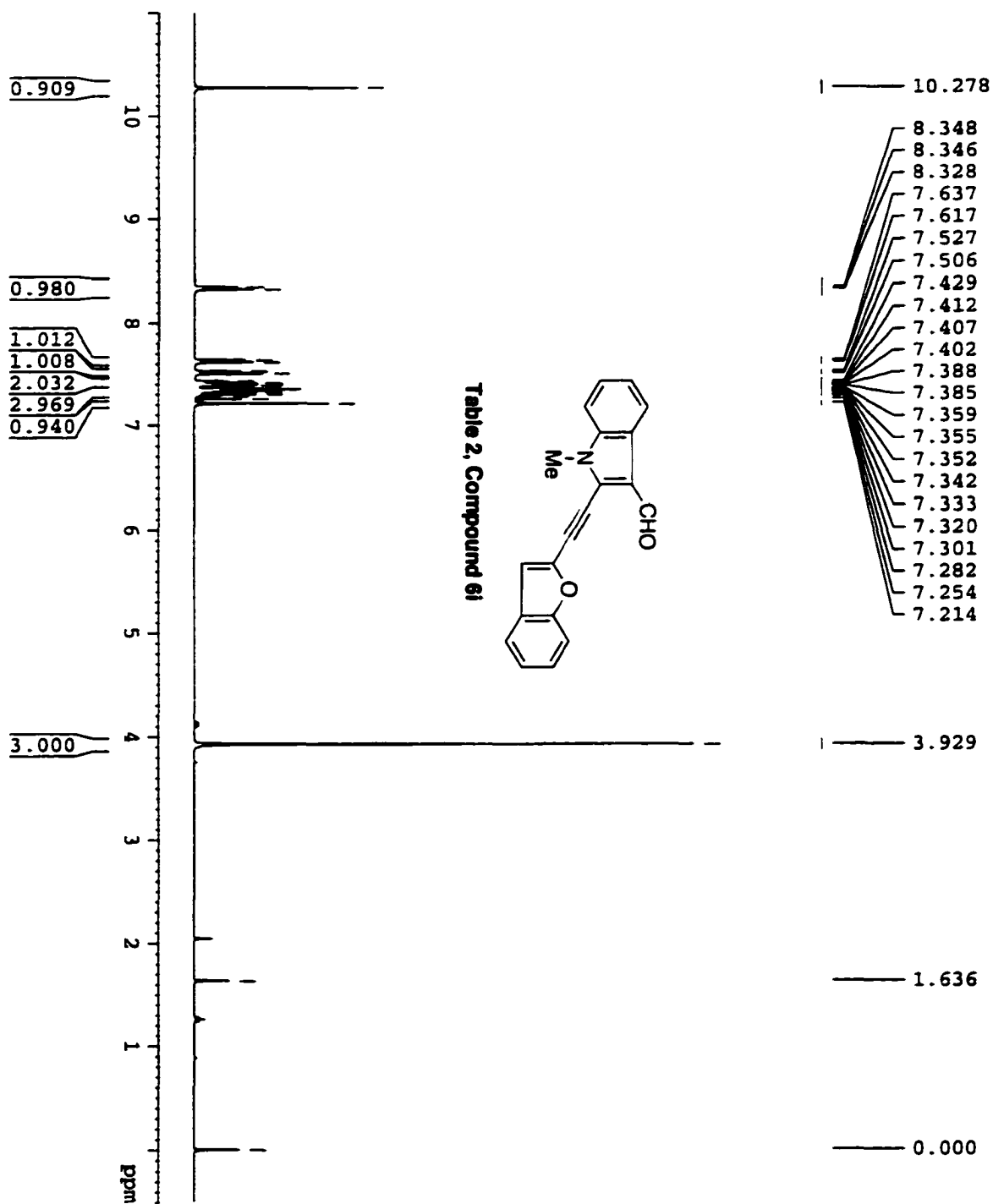


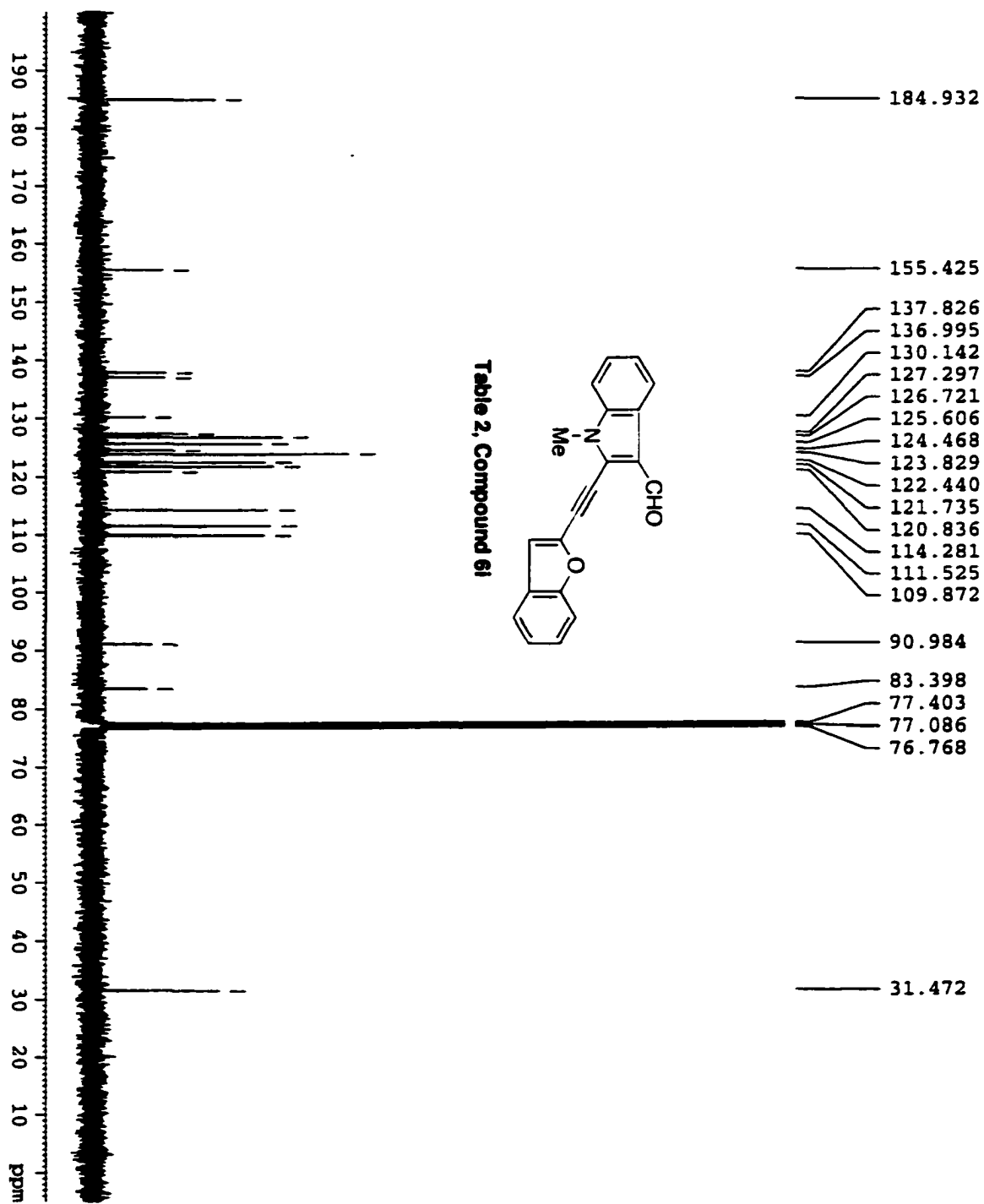


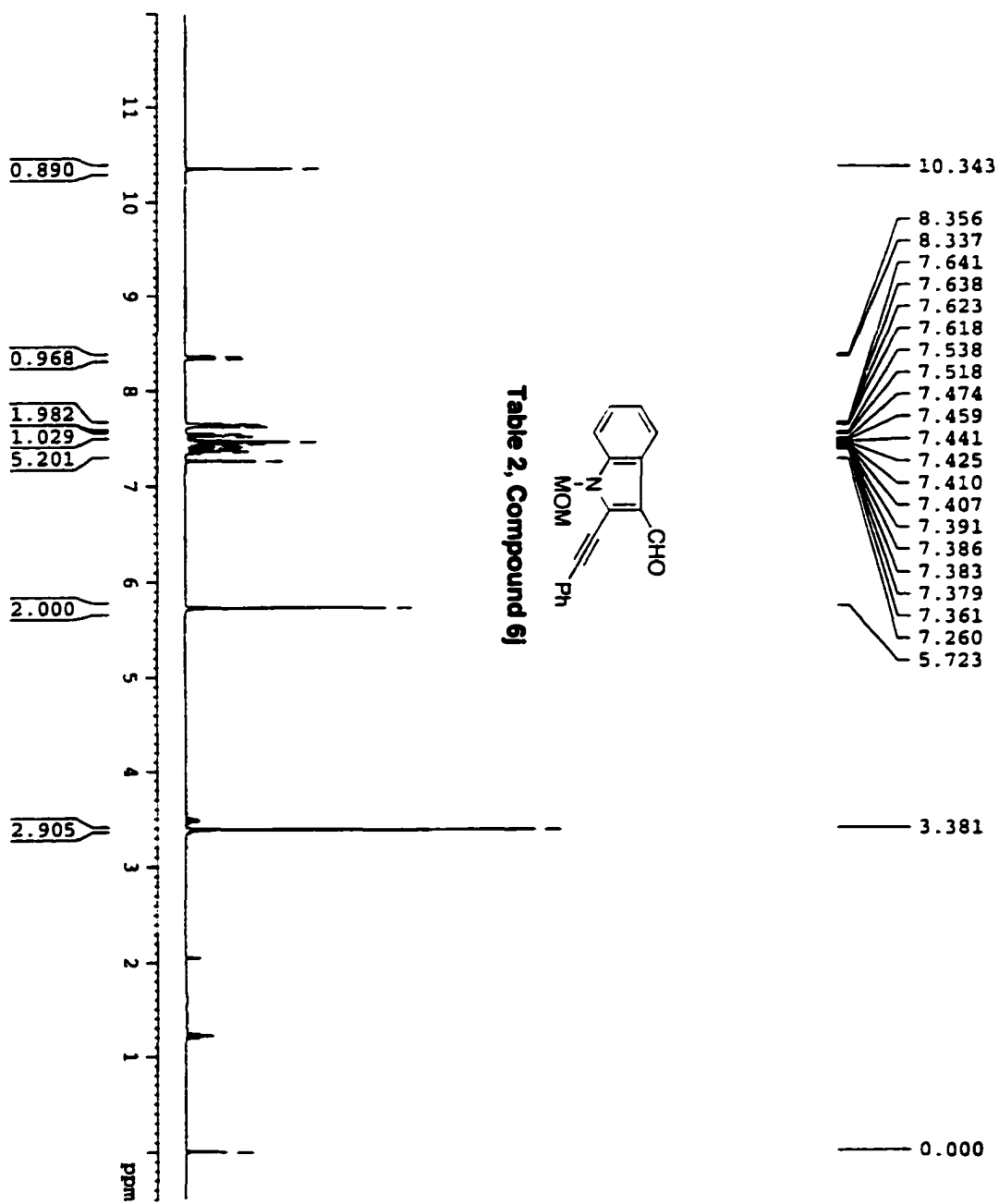


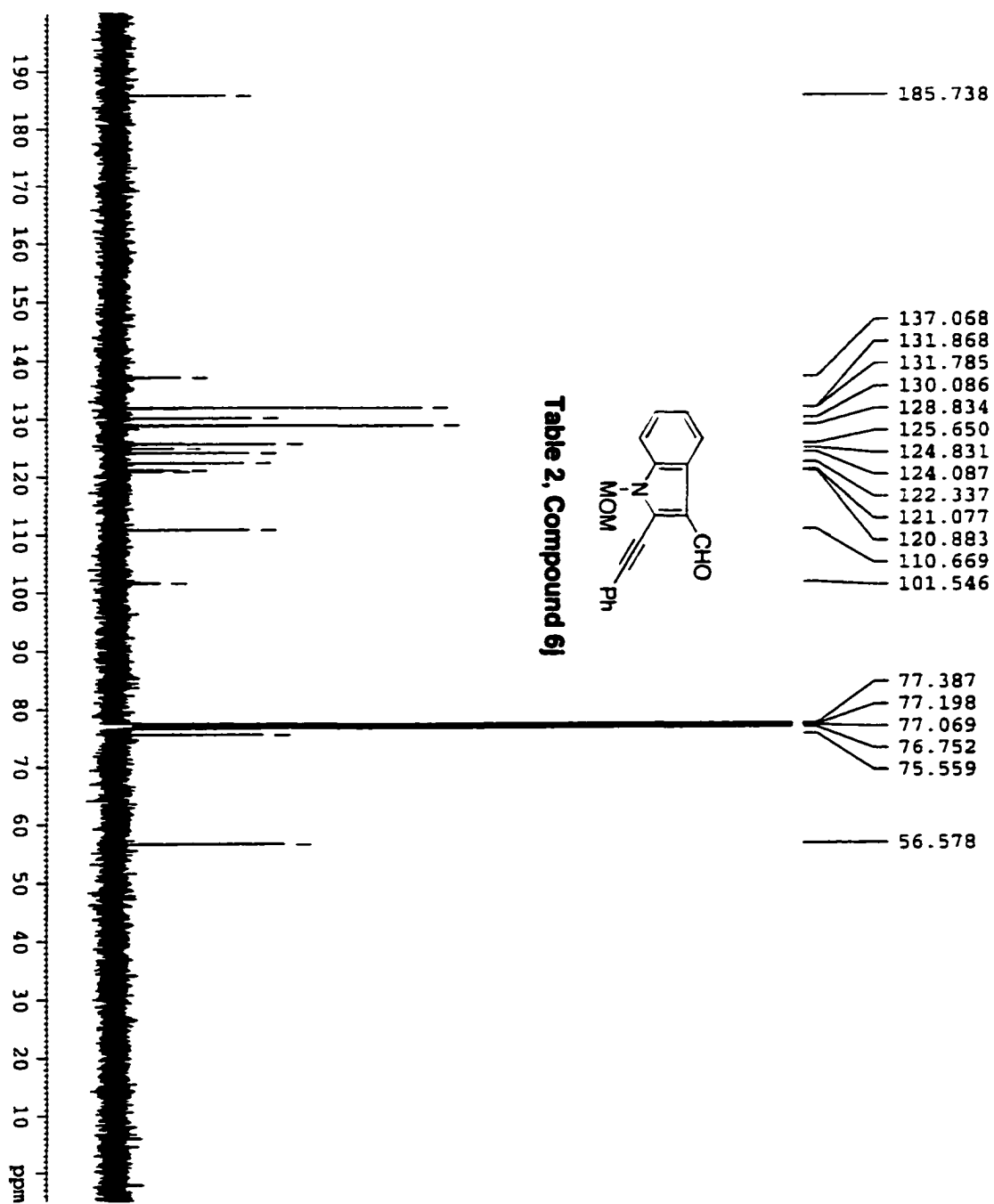




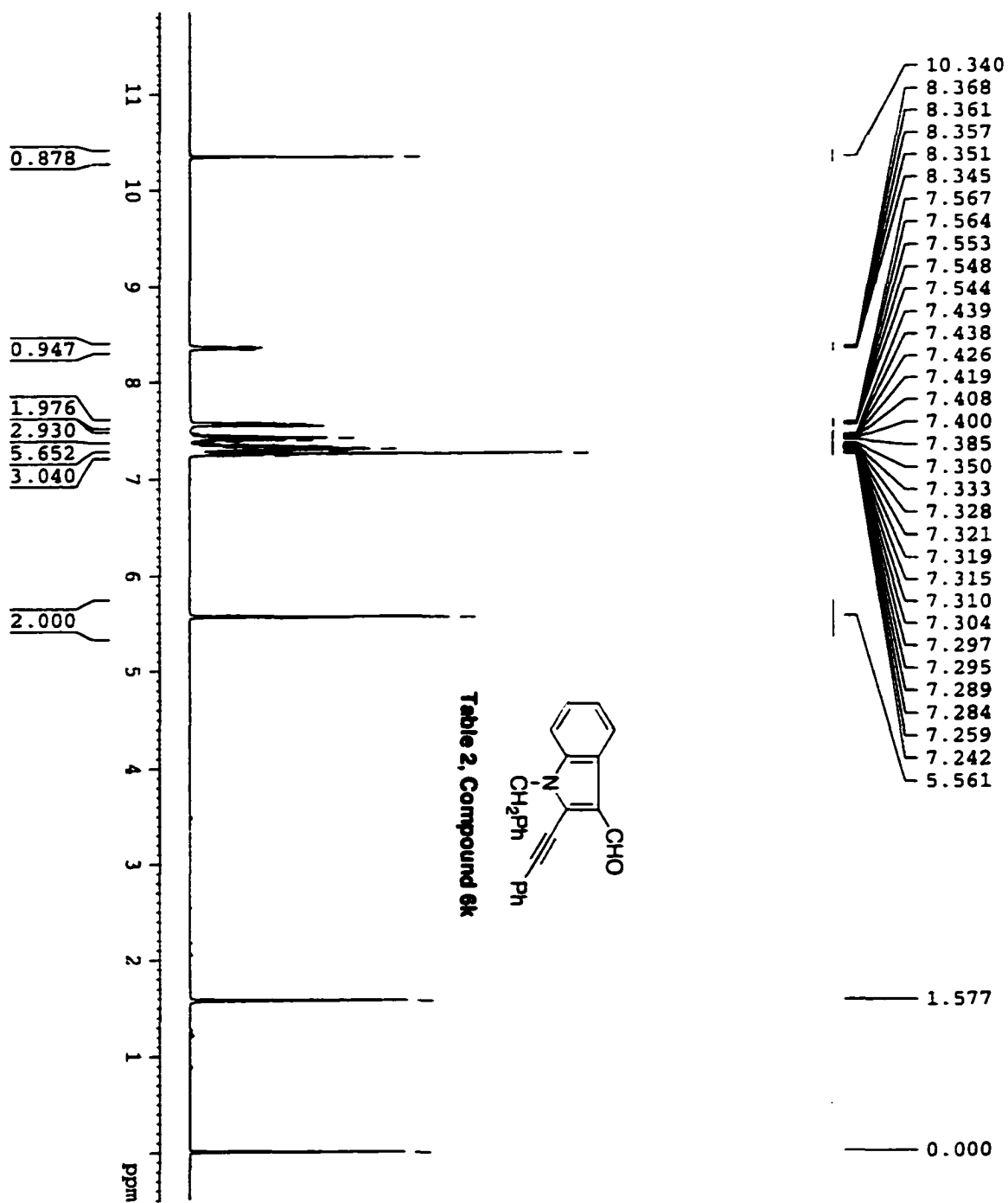


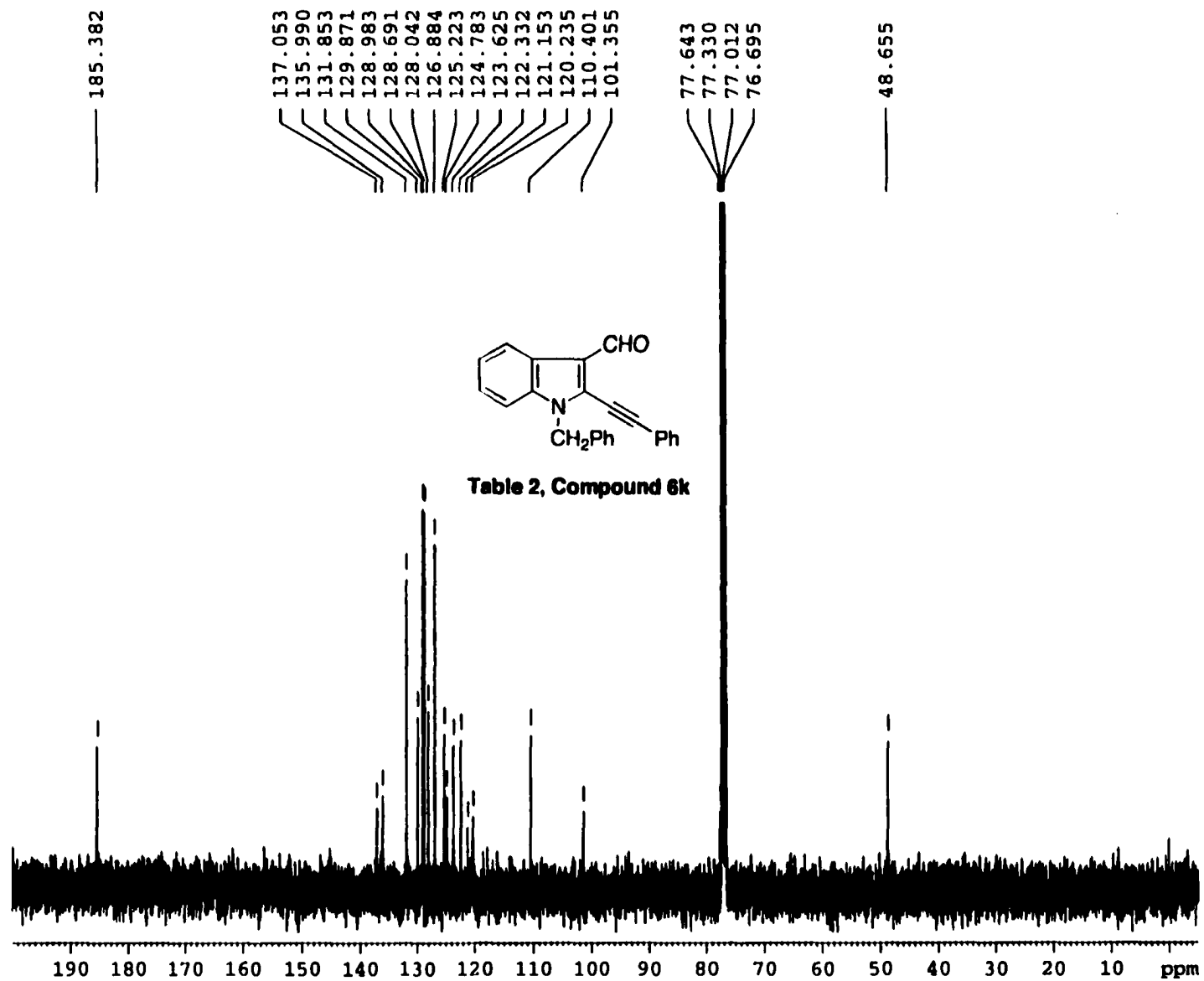












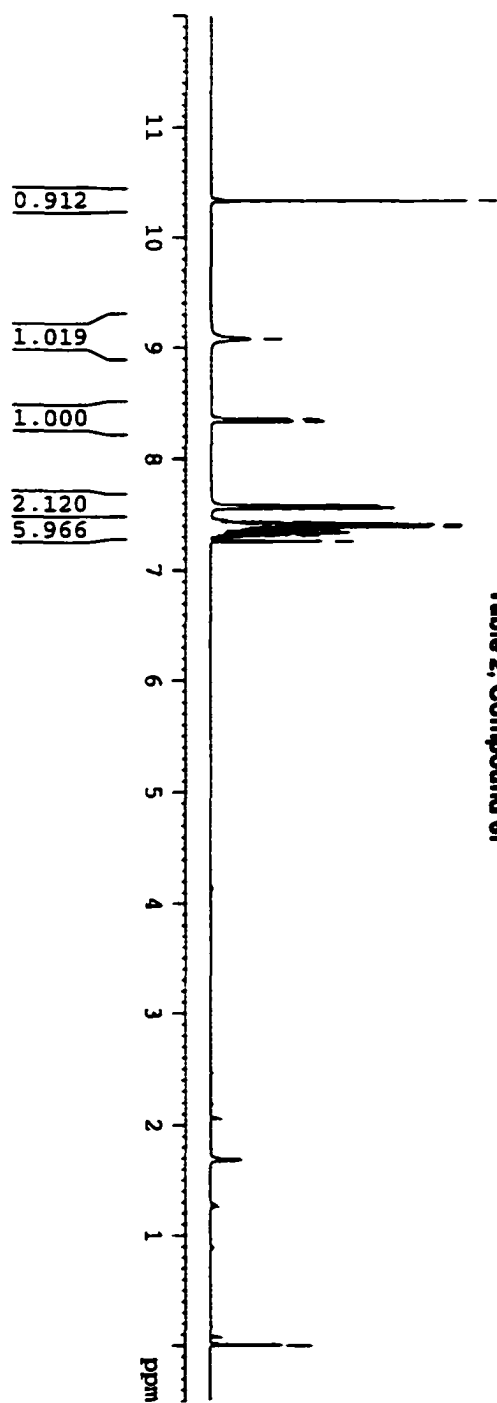
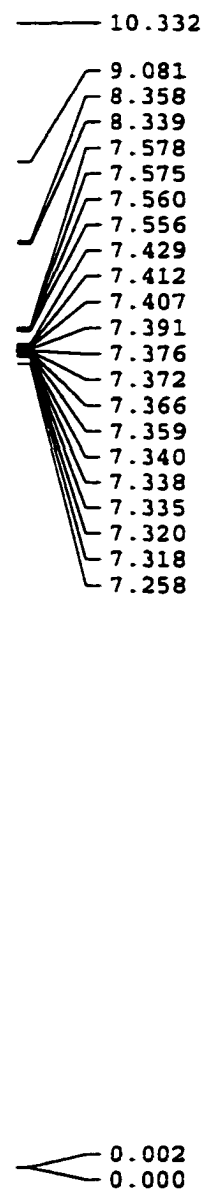
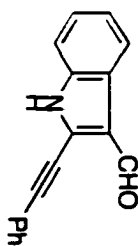
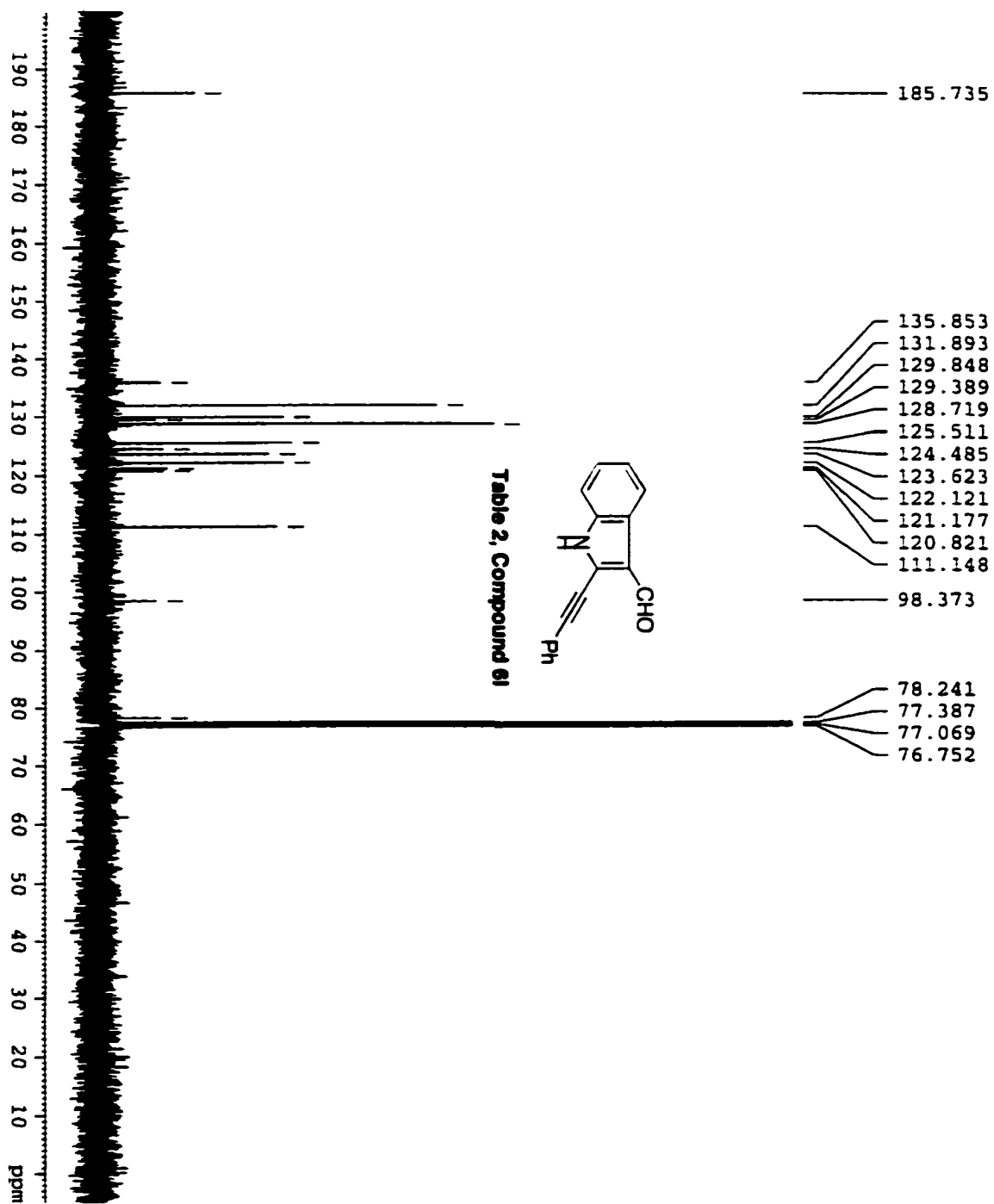
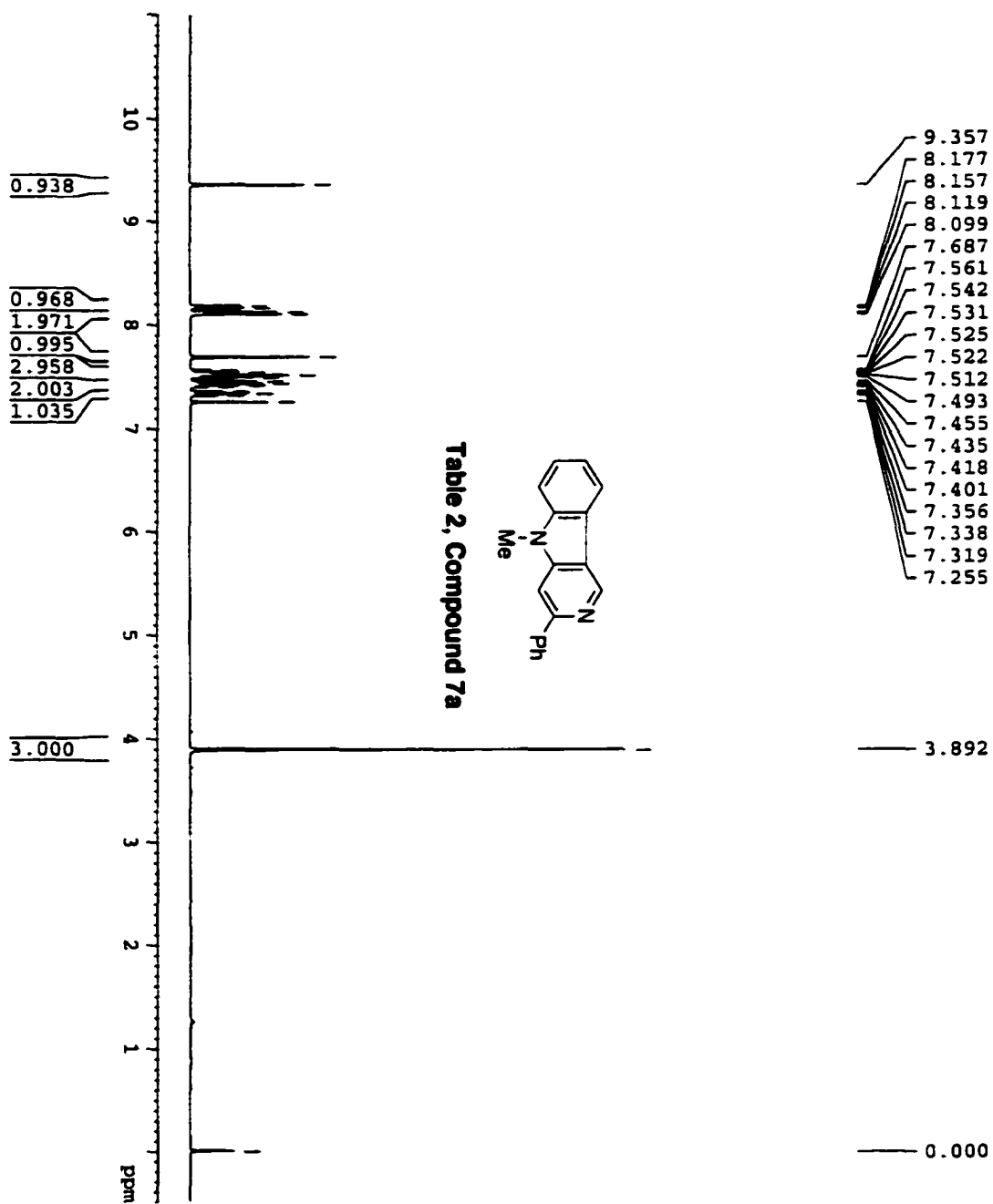
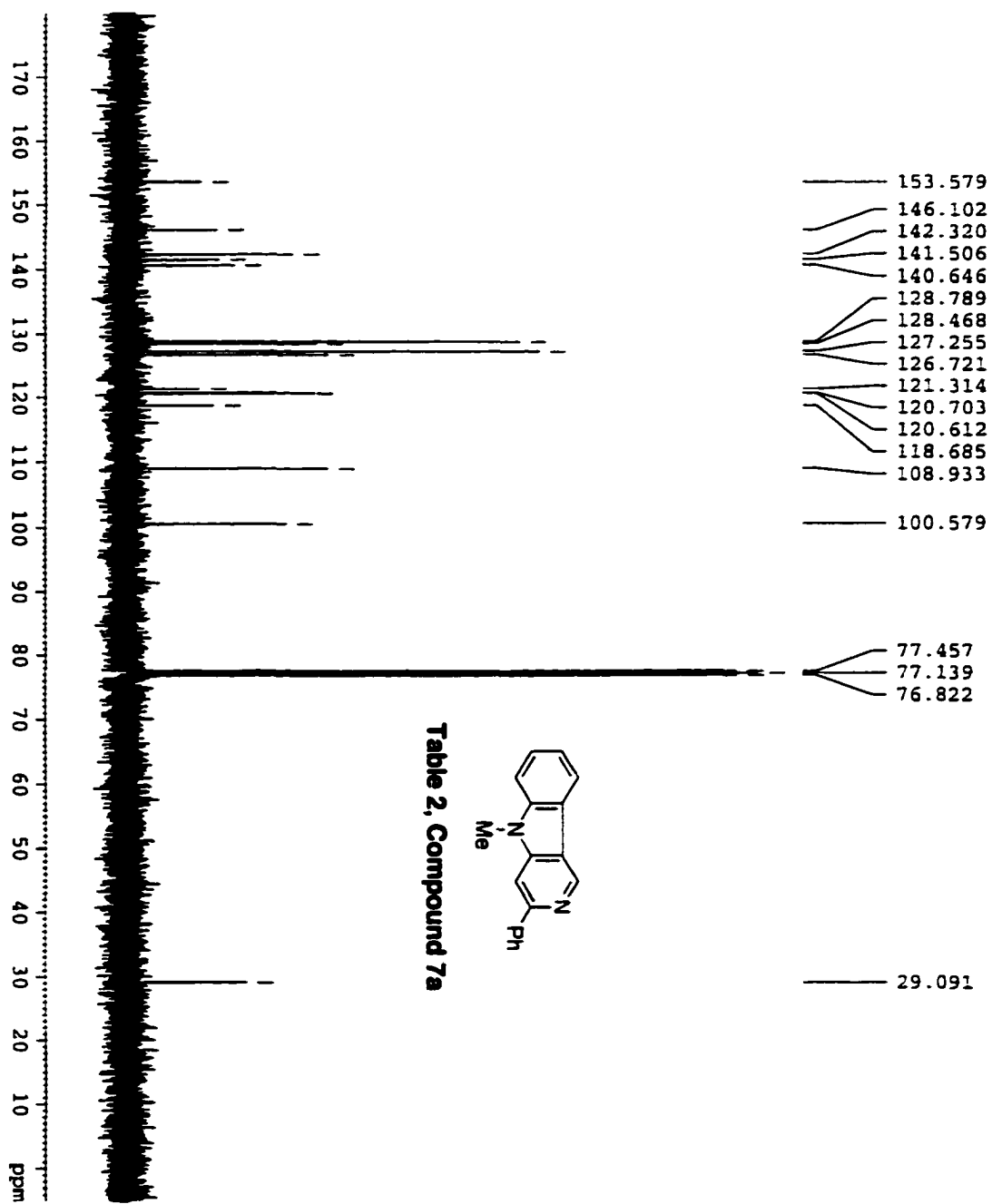


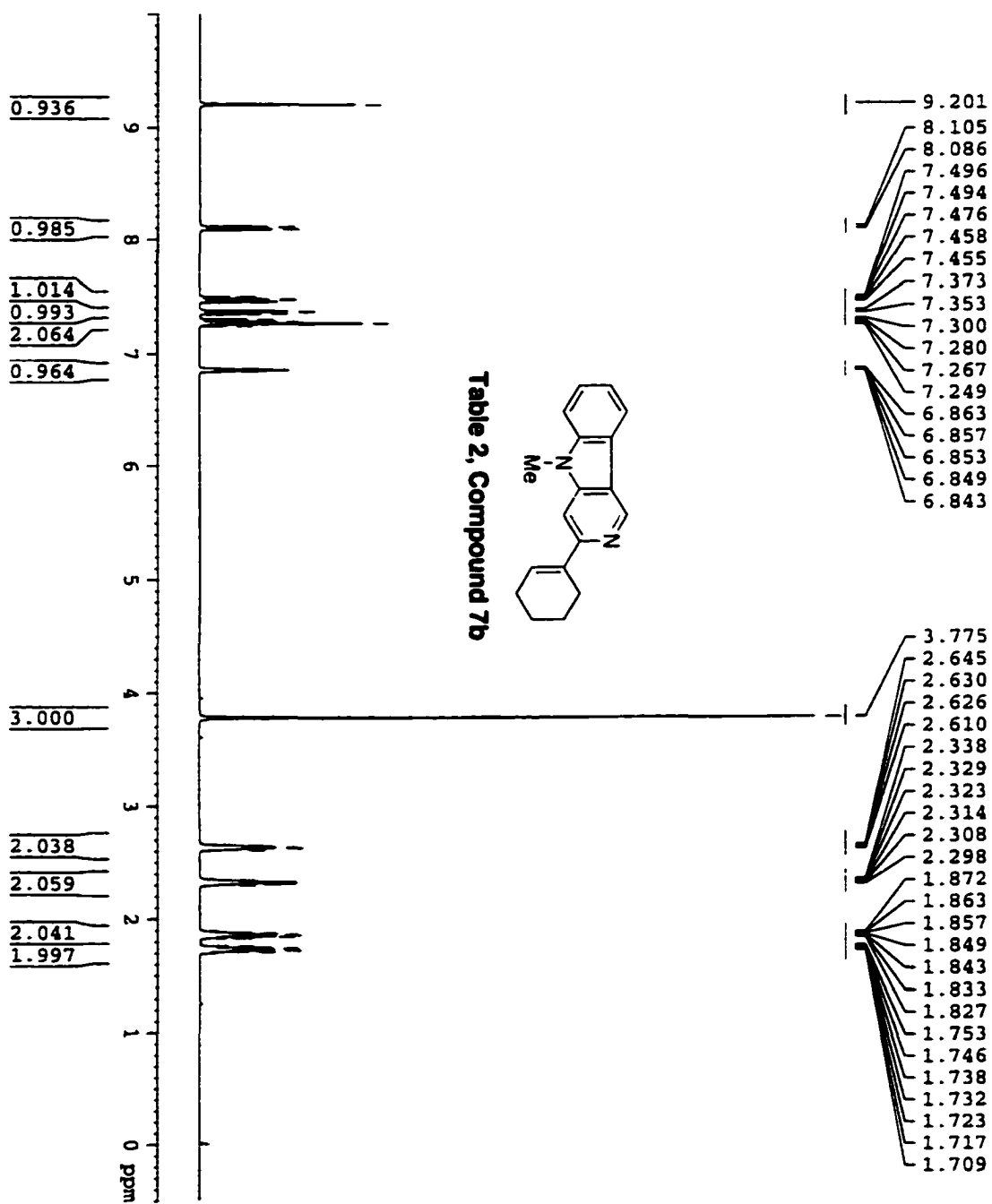
Table 2, Compound 61

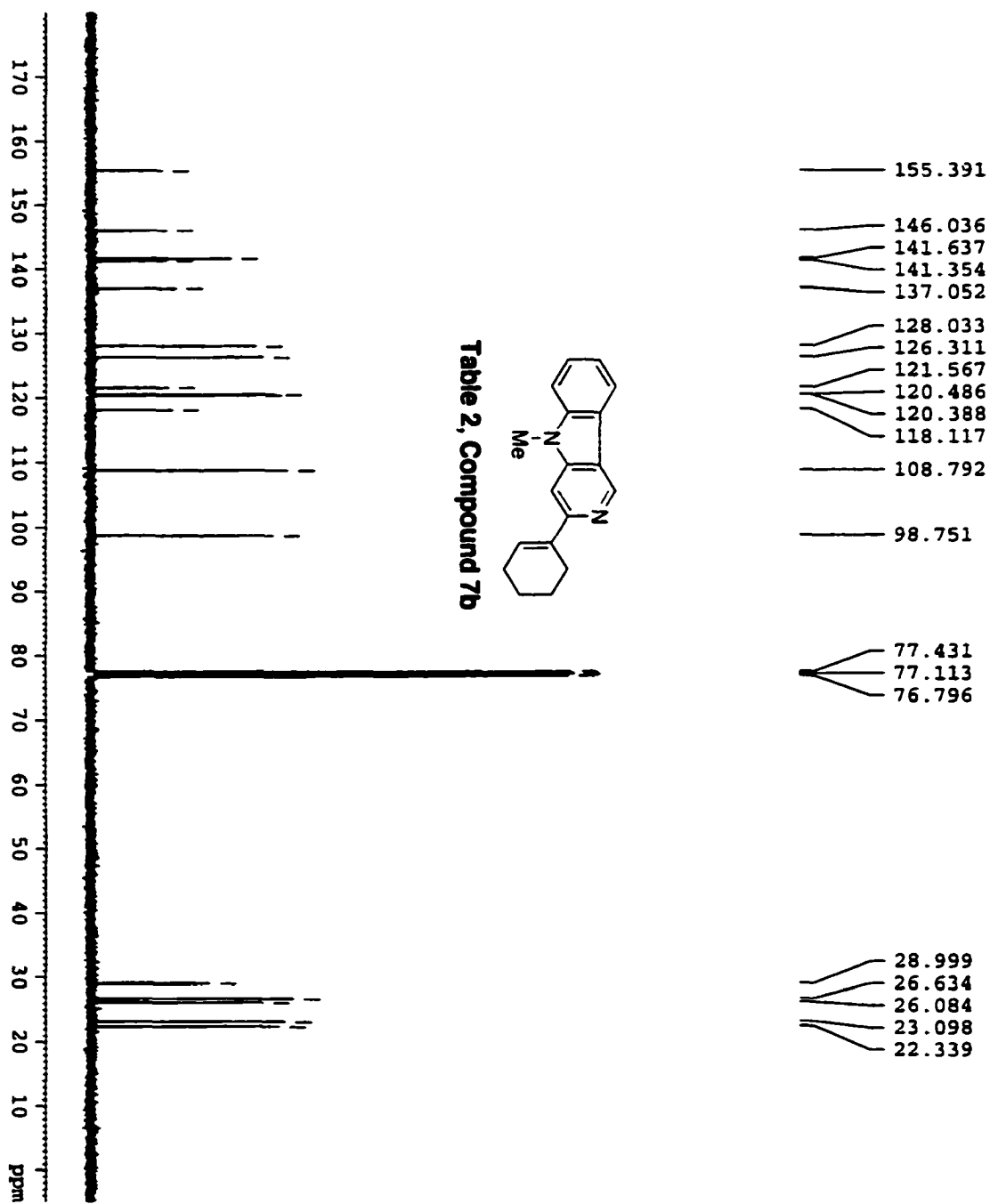




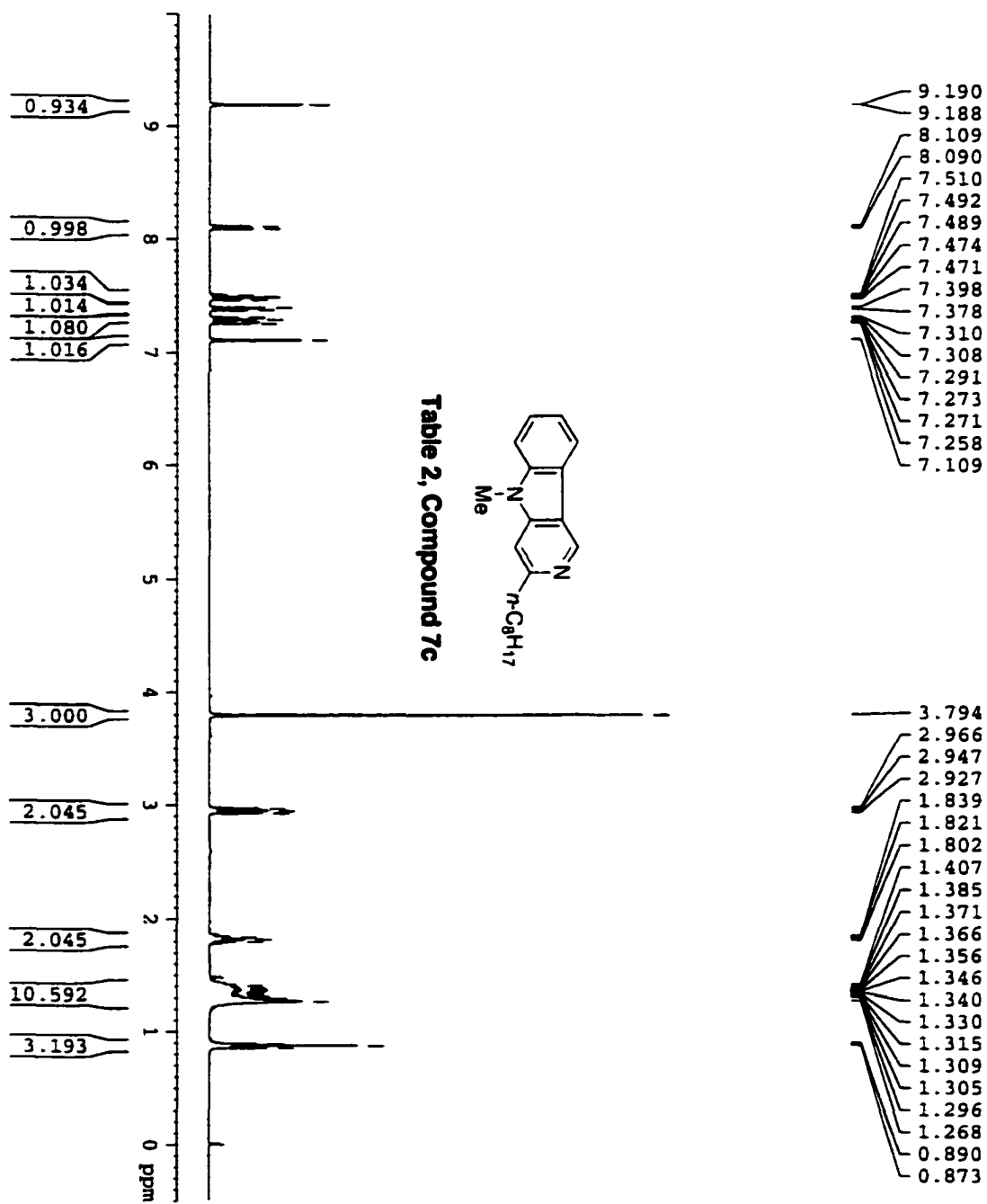


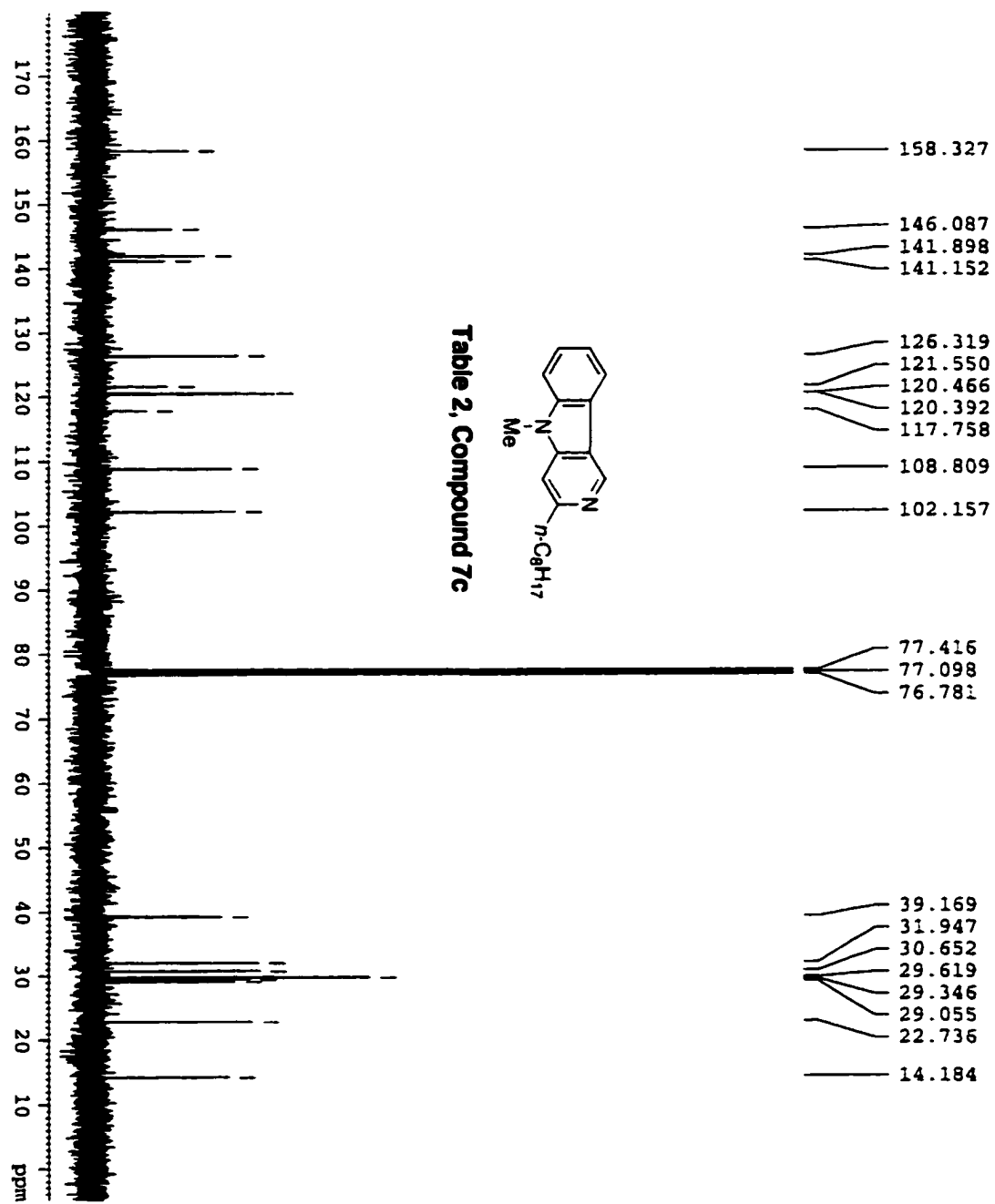


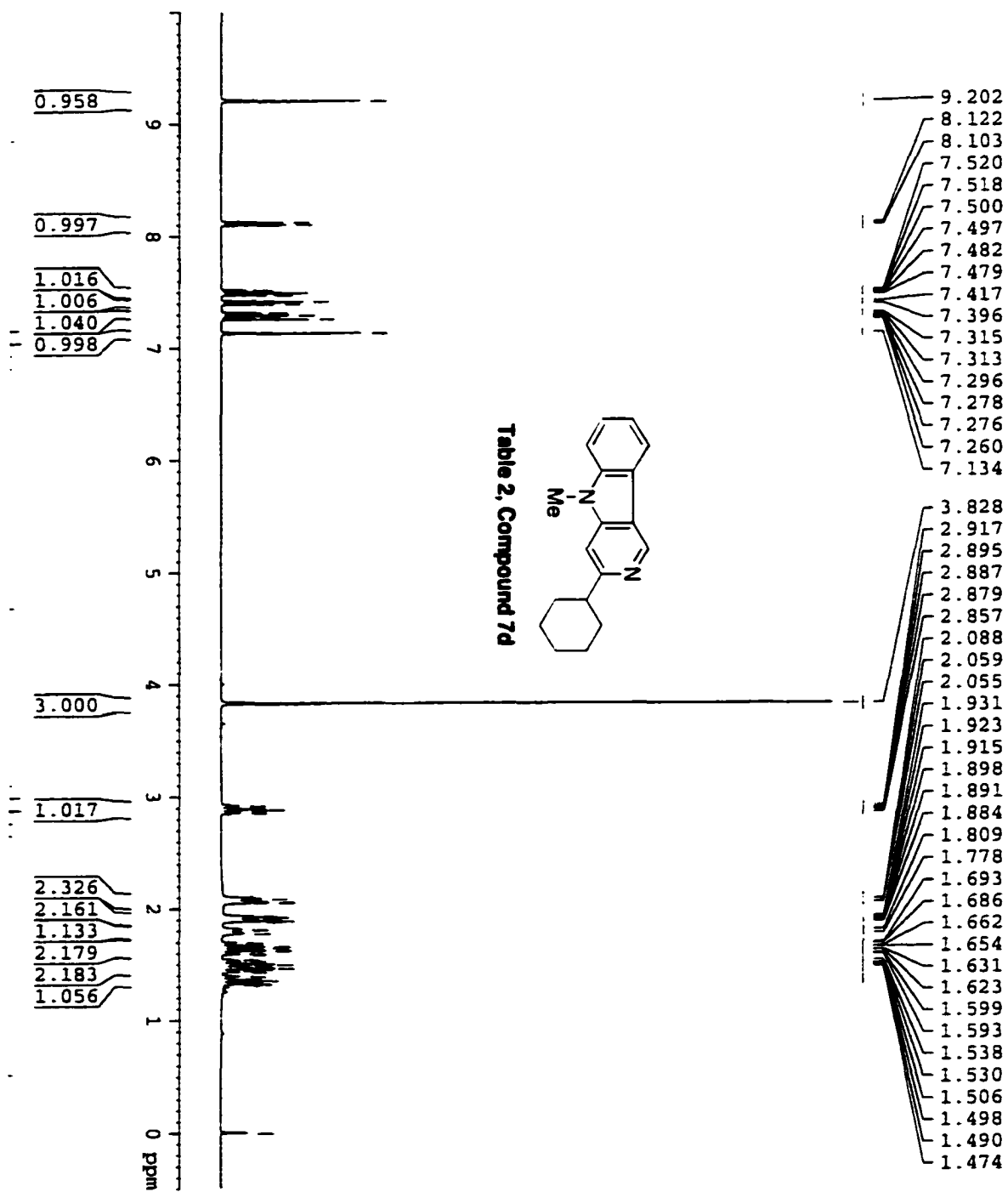


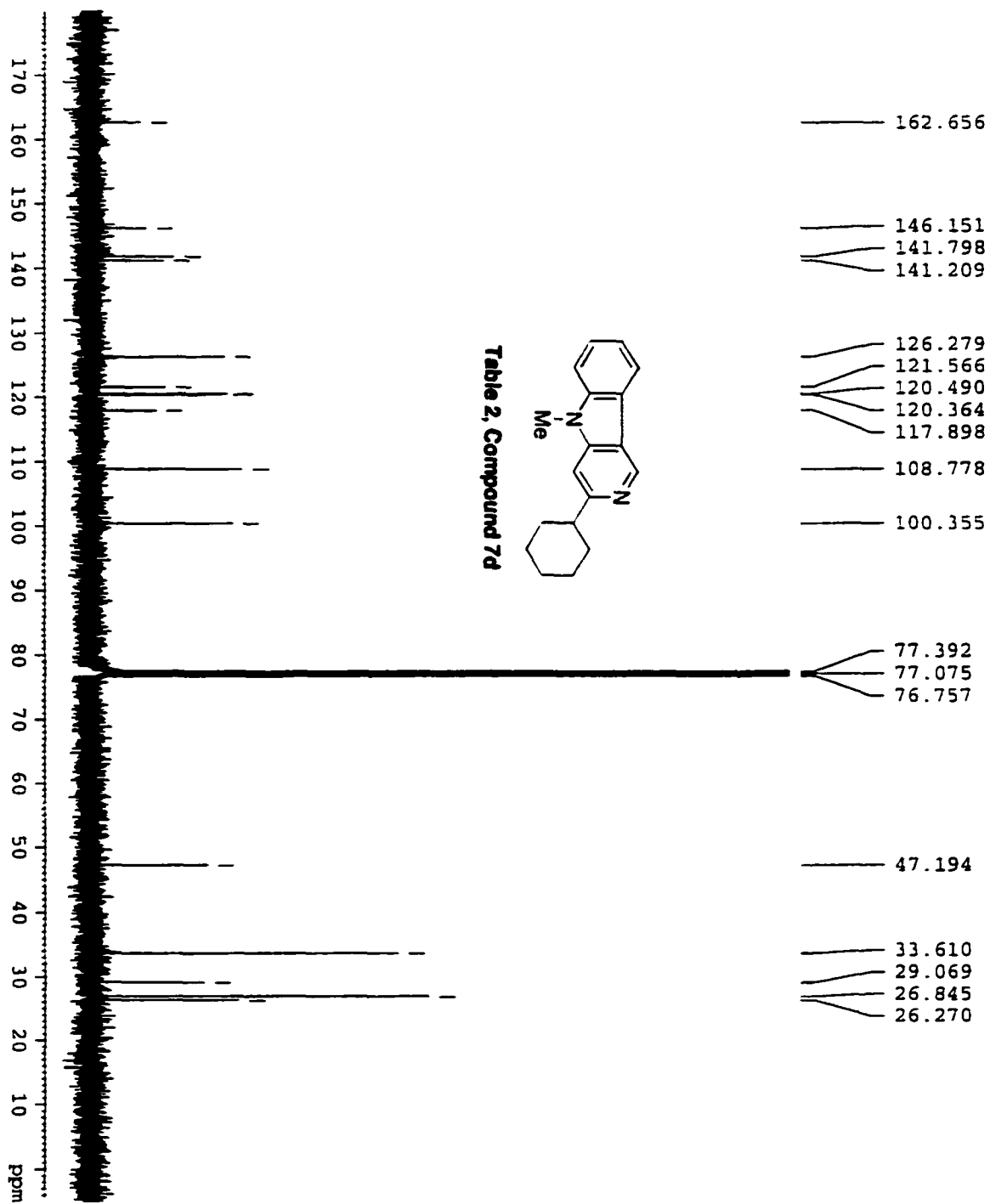


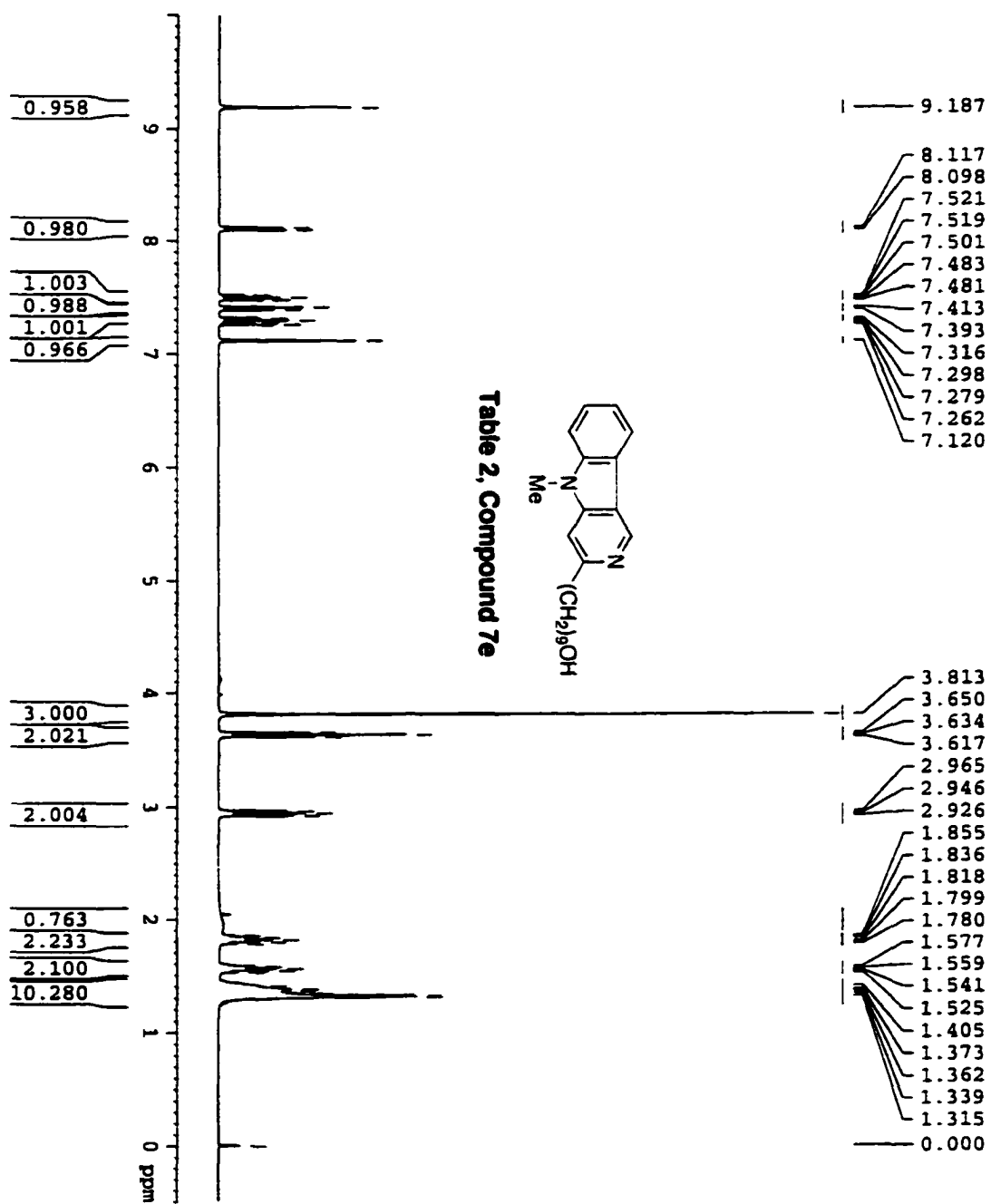


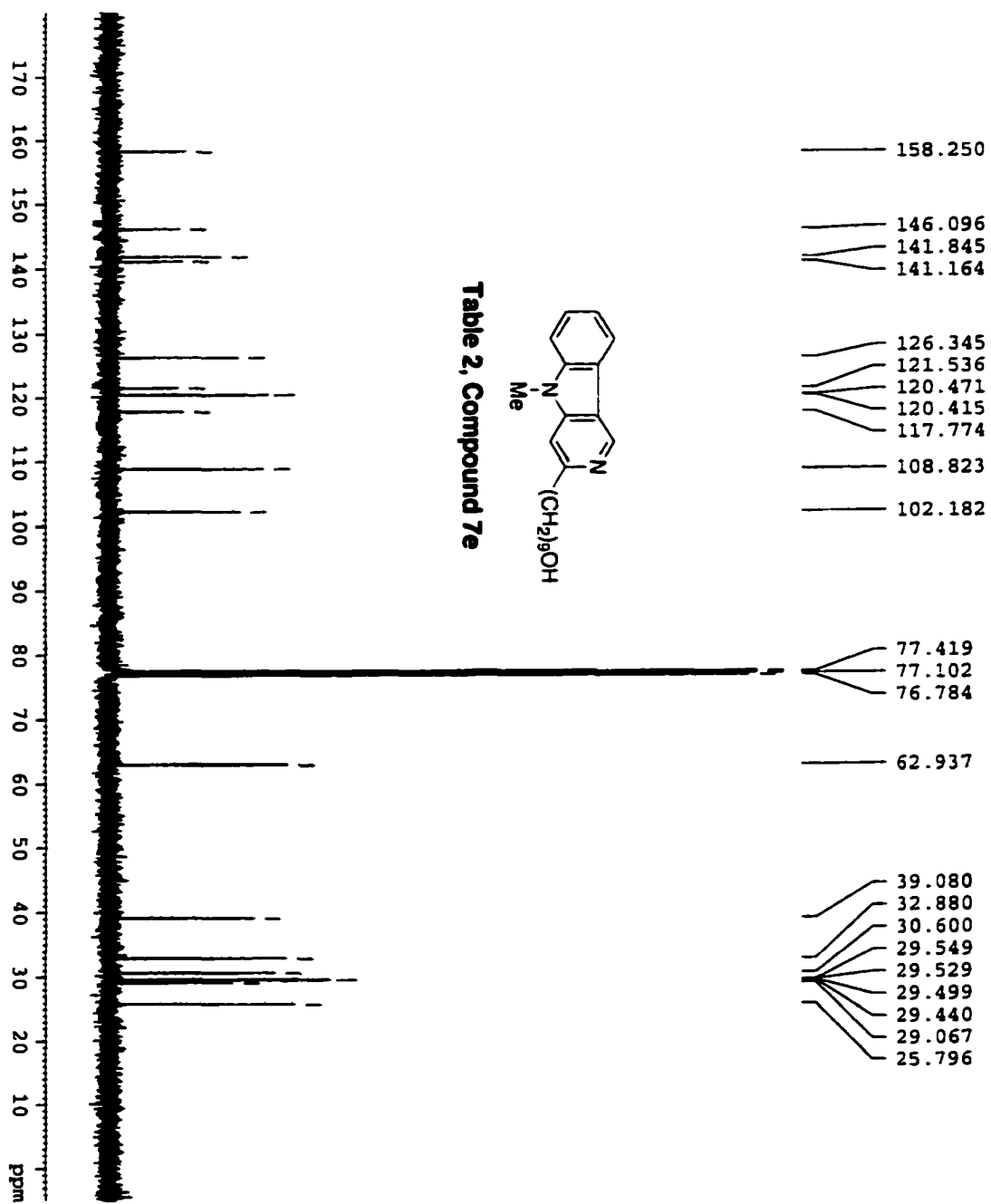


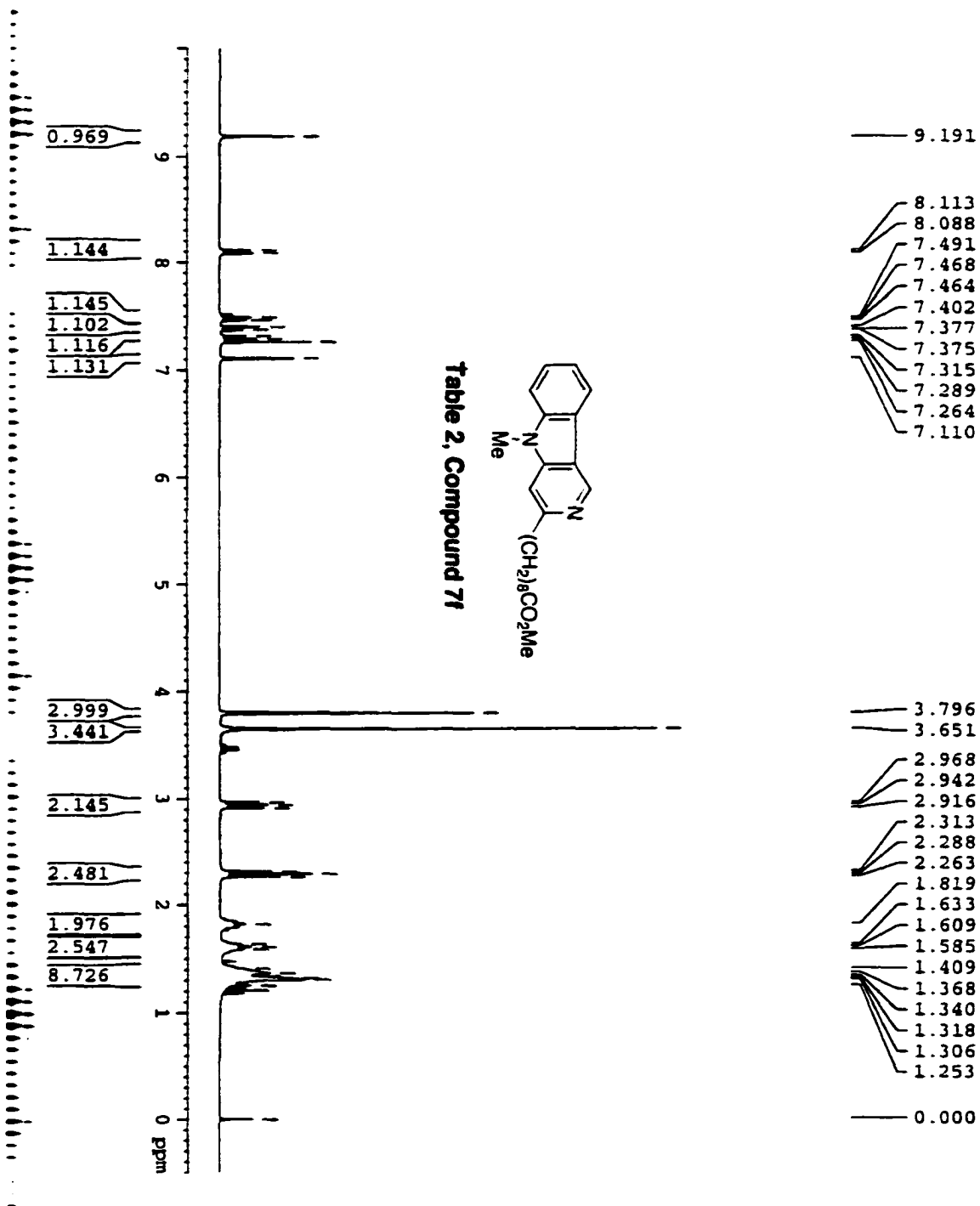












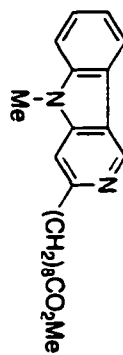
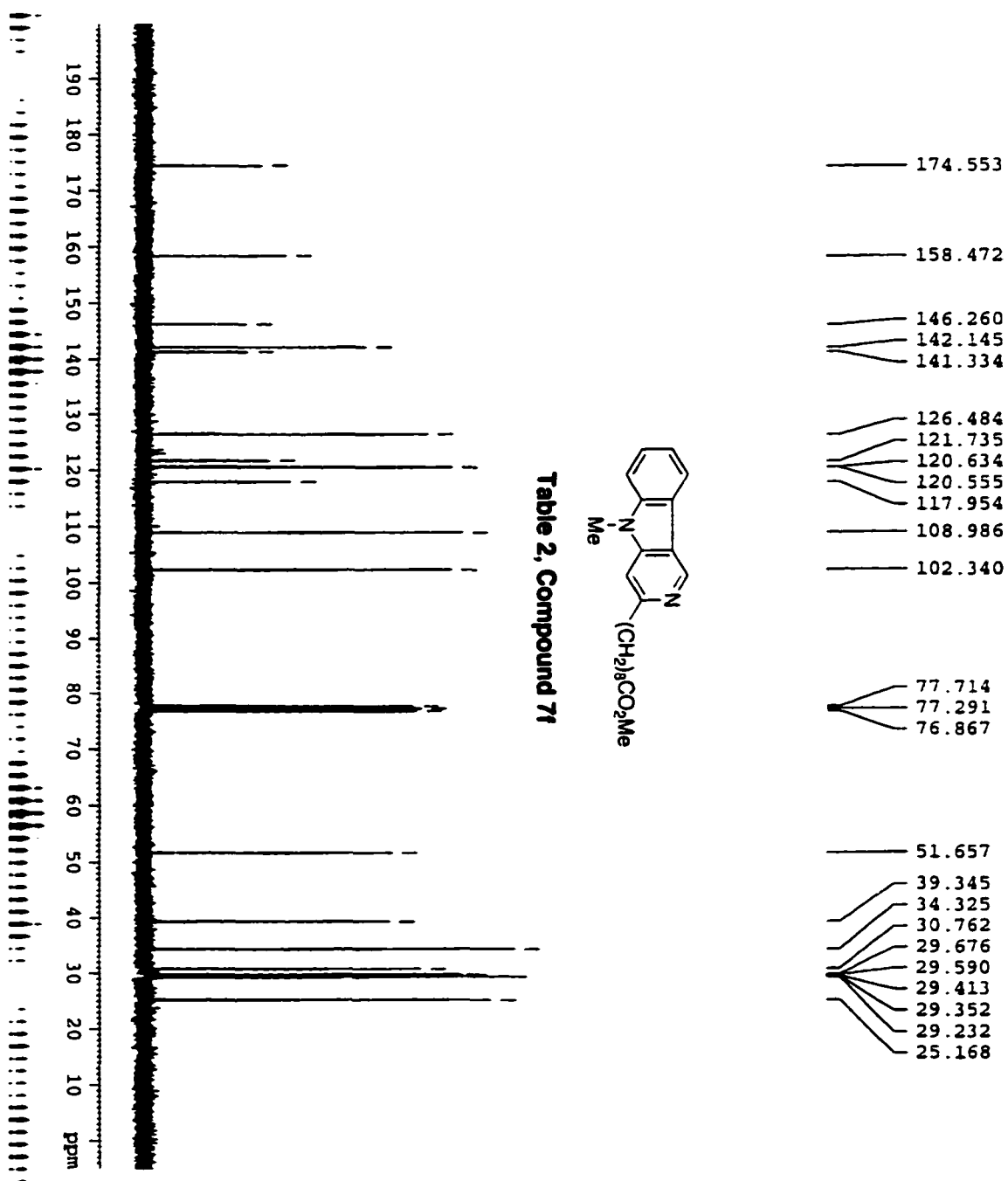
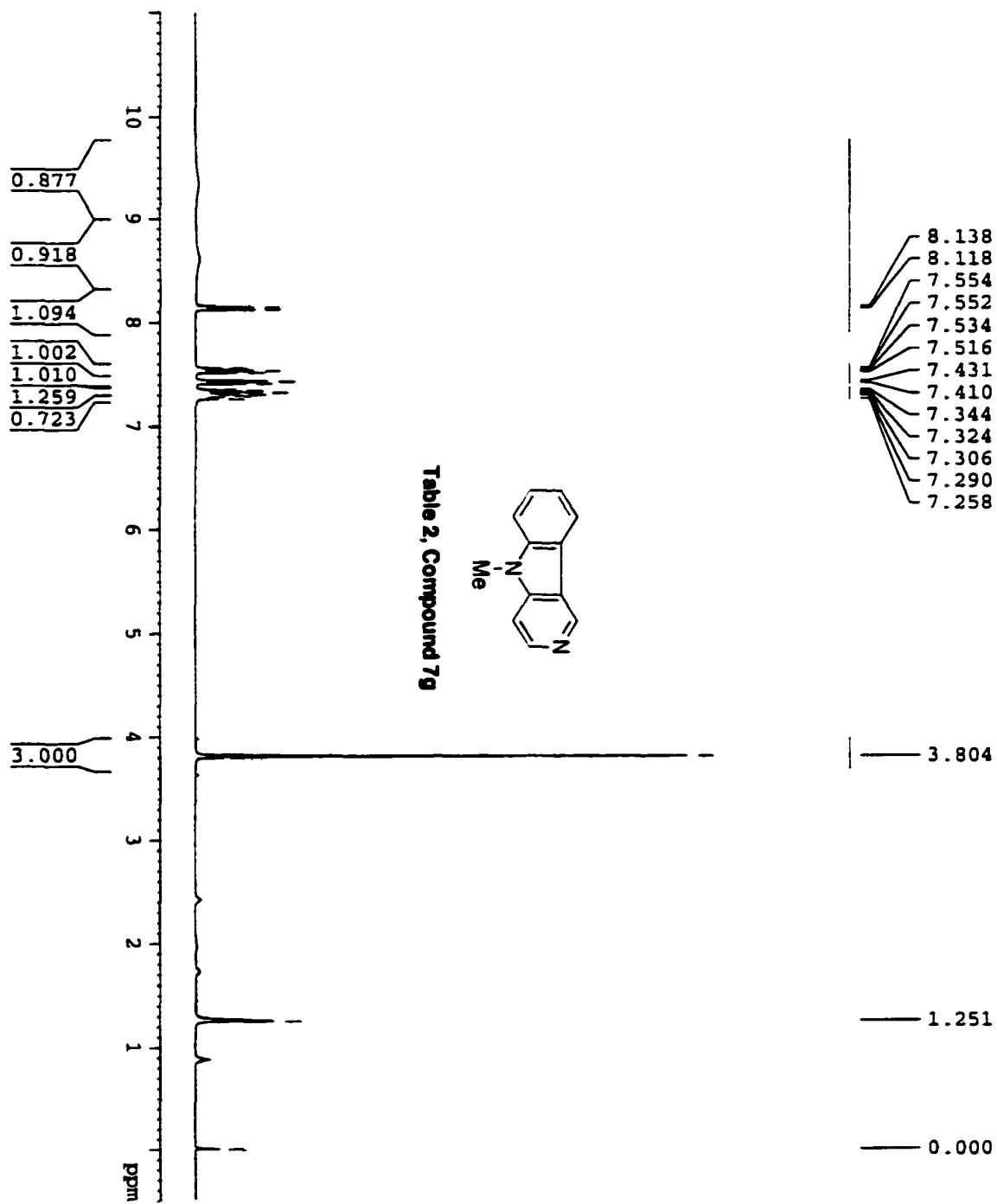
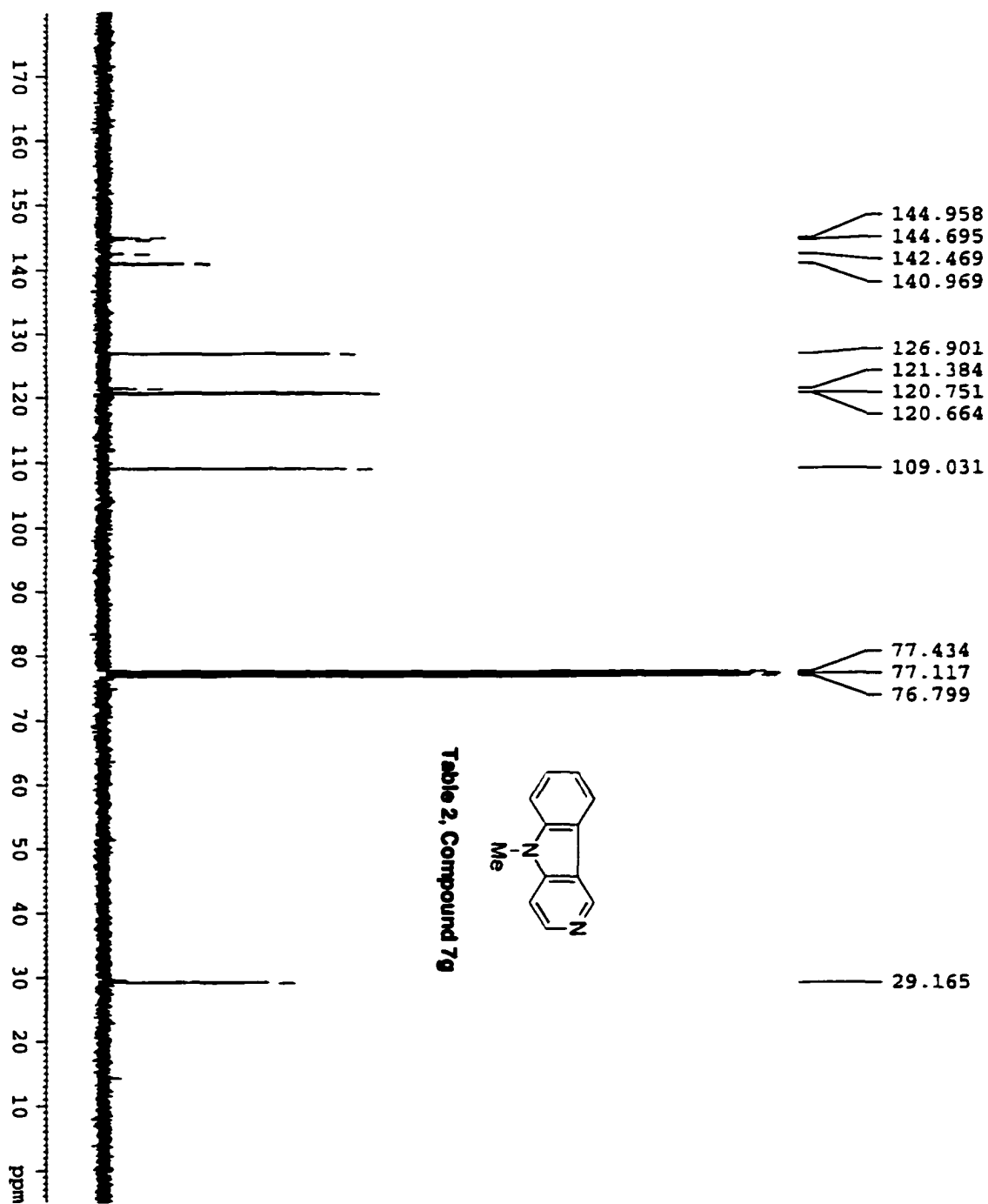


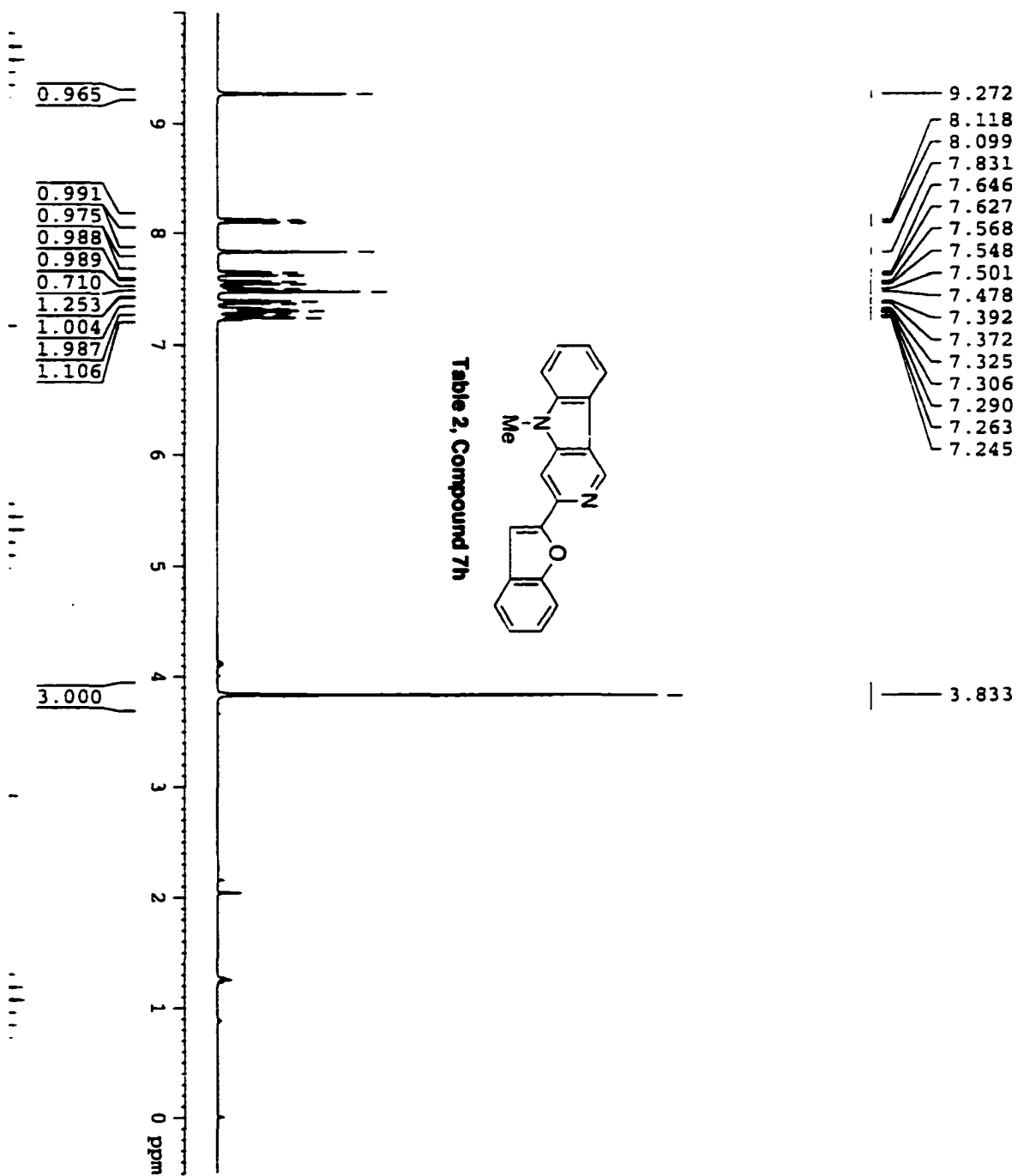
Table 2, Compound 7i

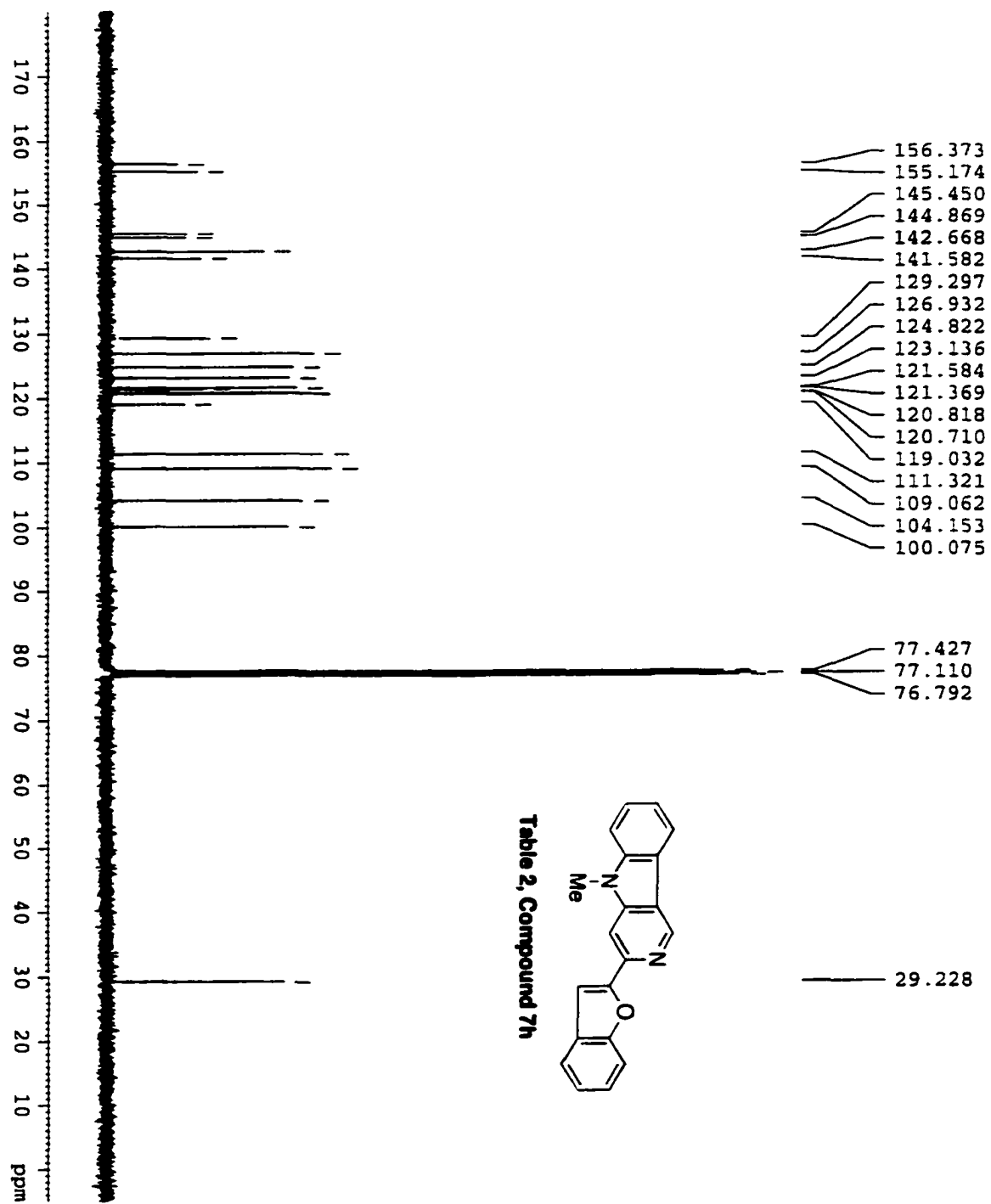


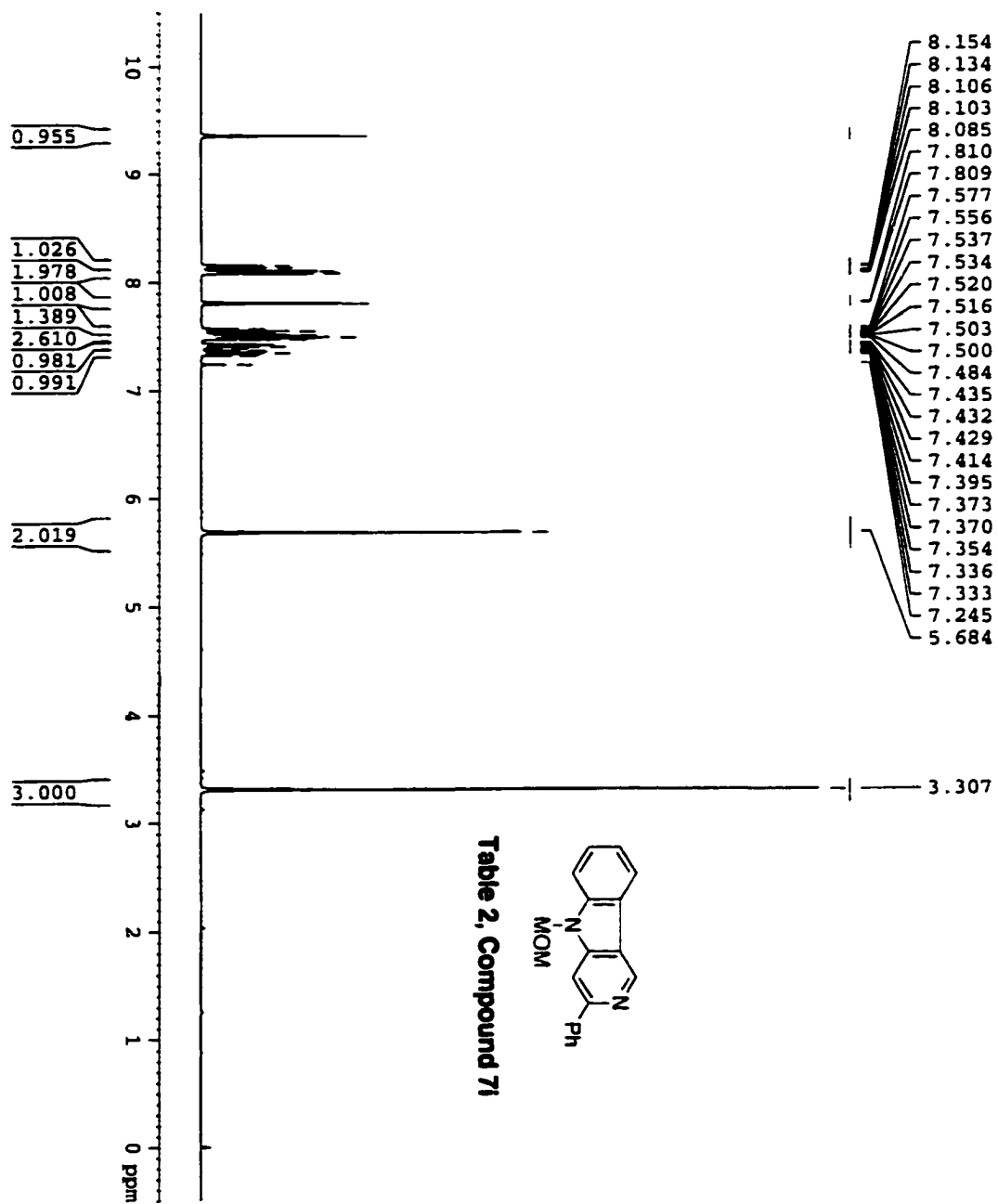


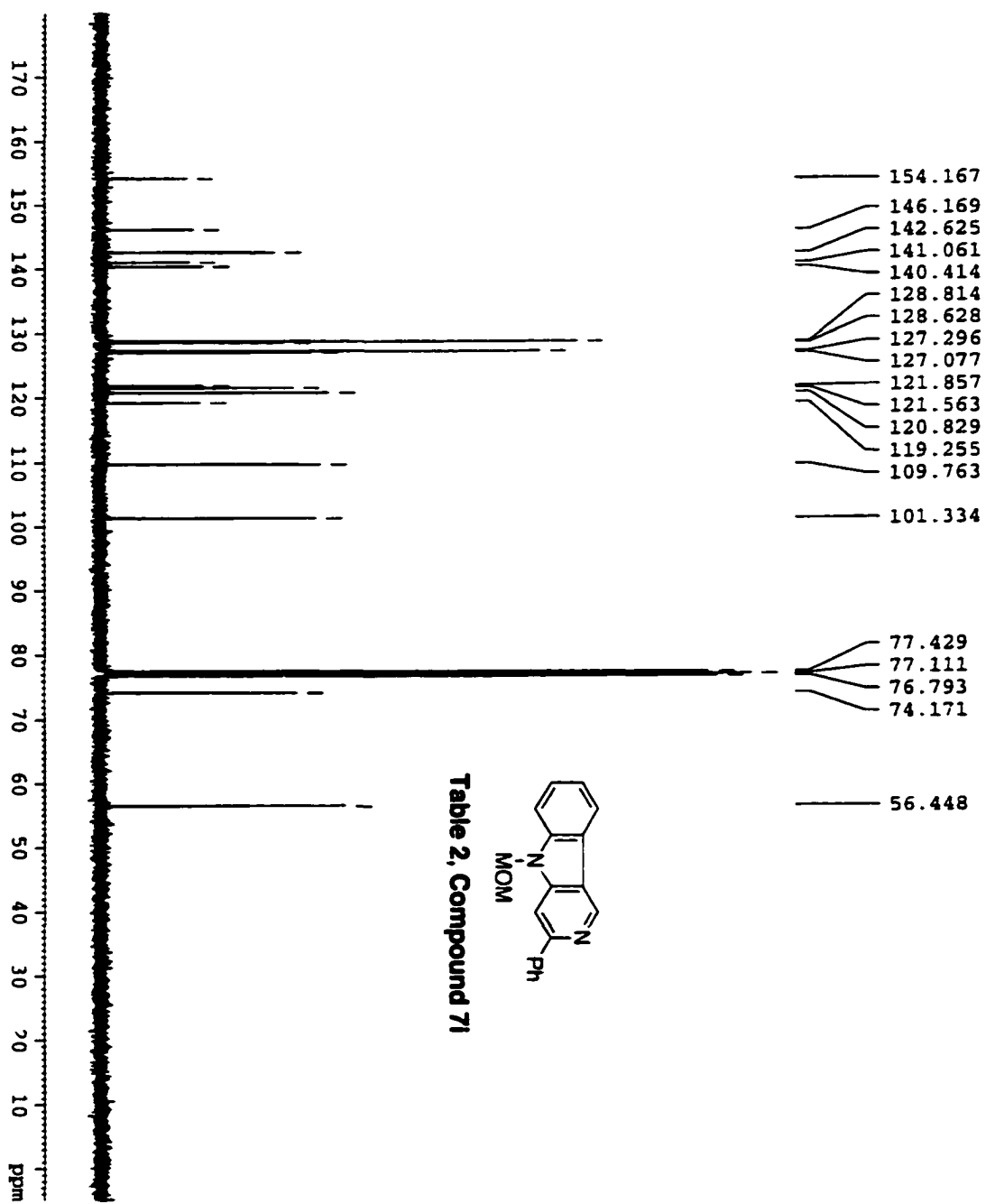


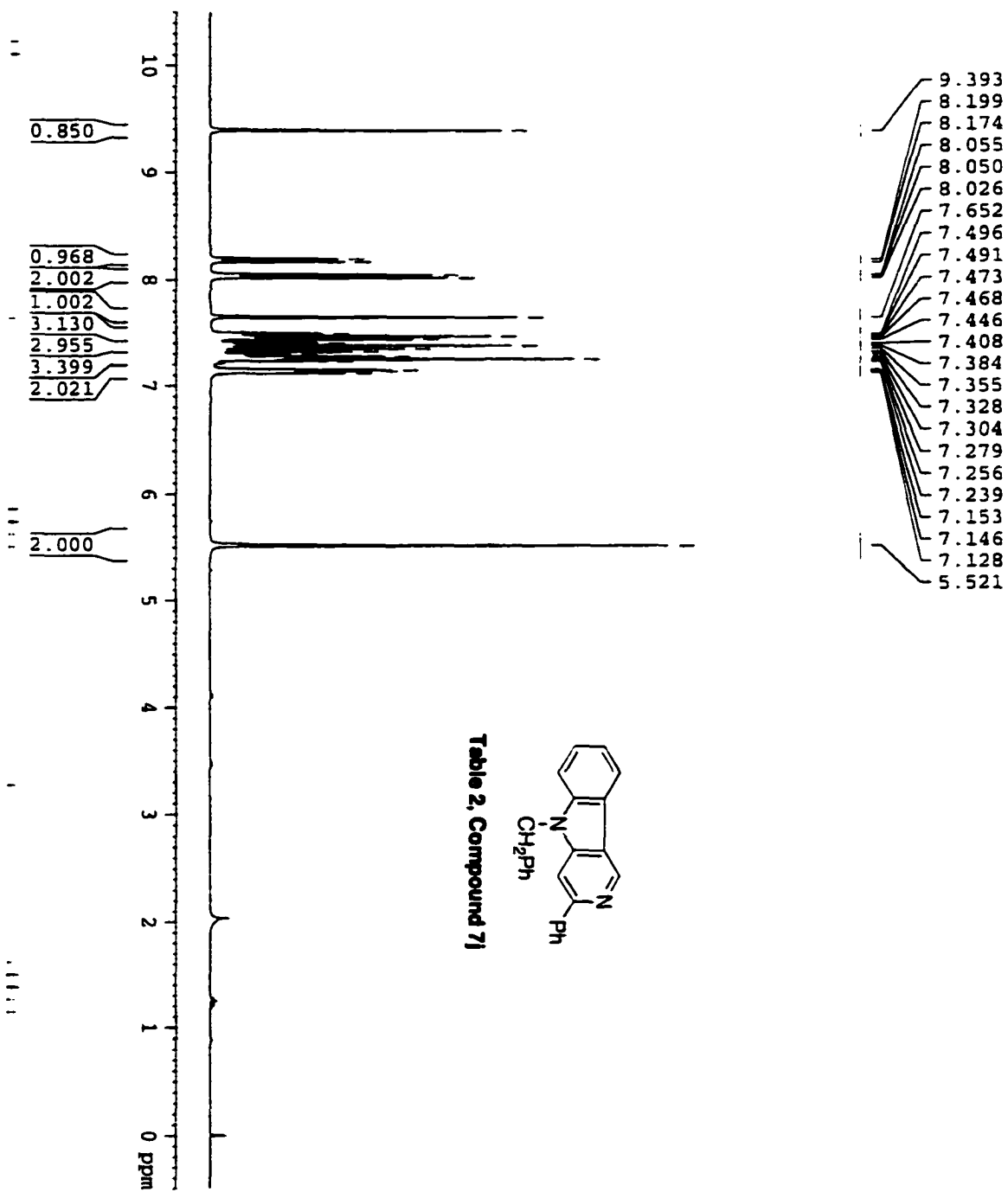


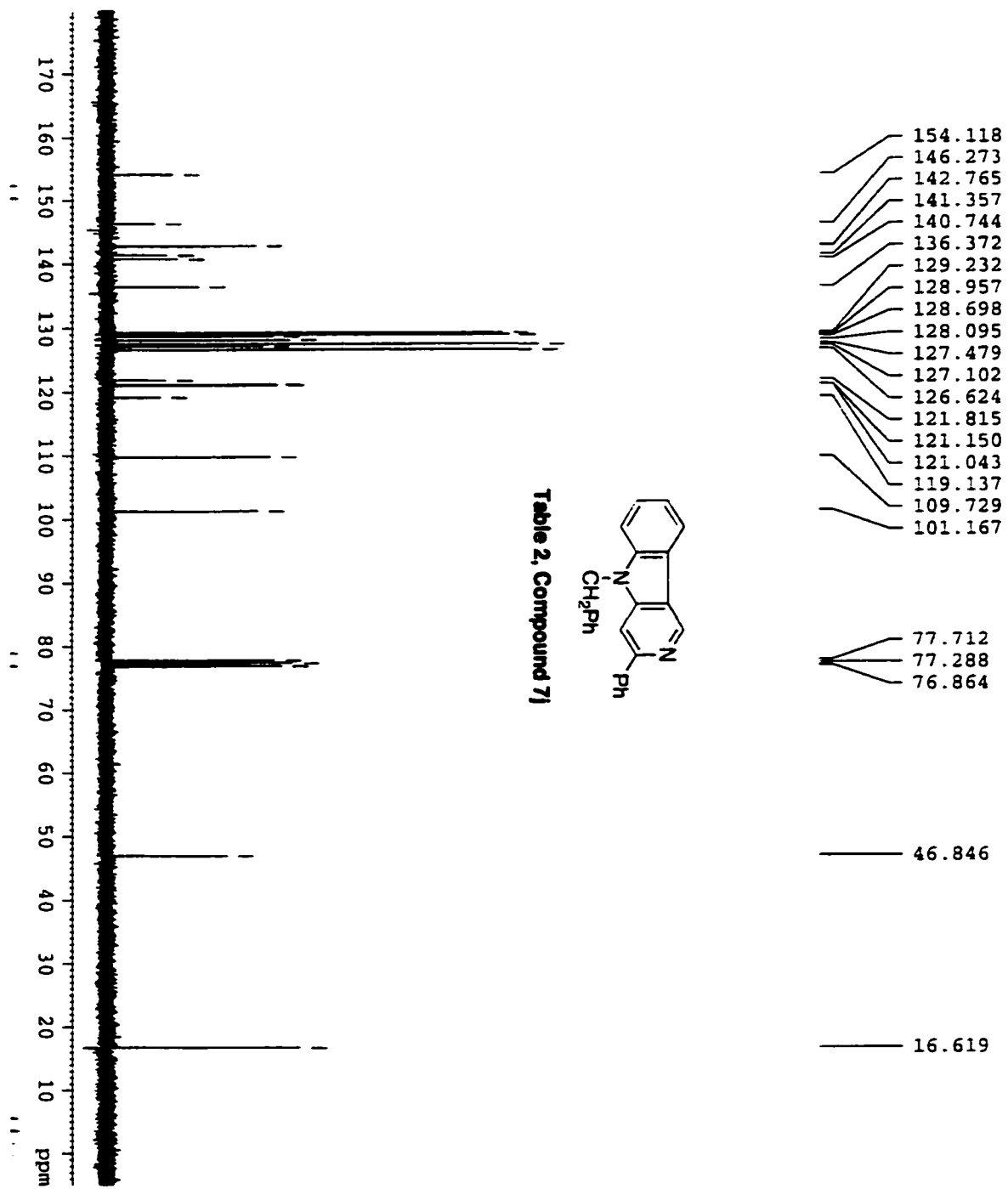




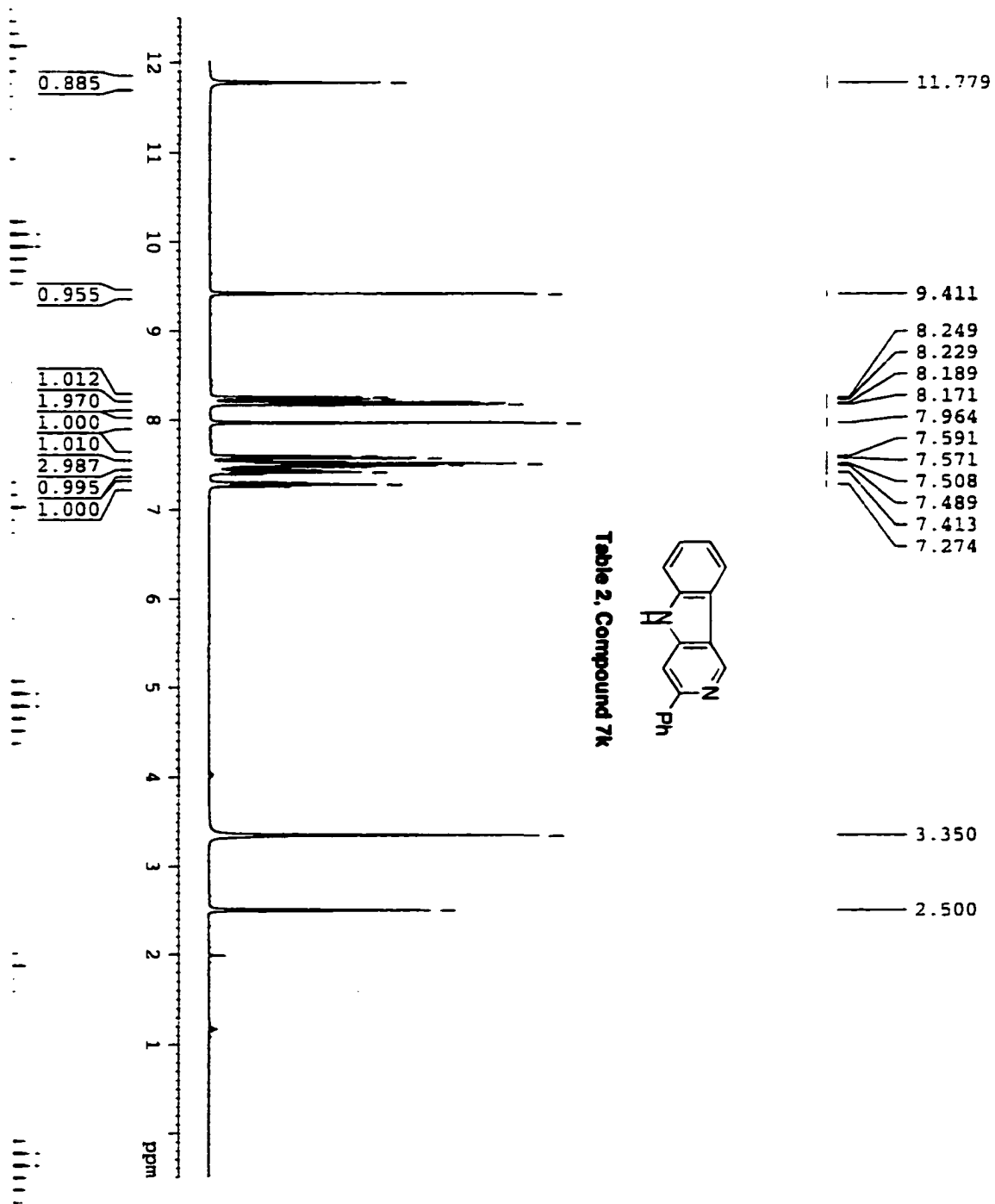


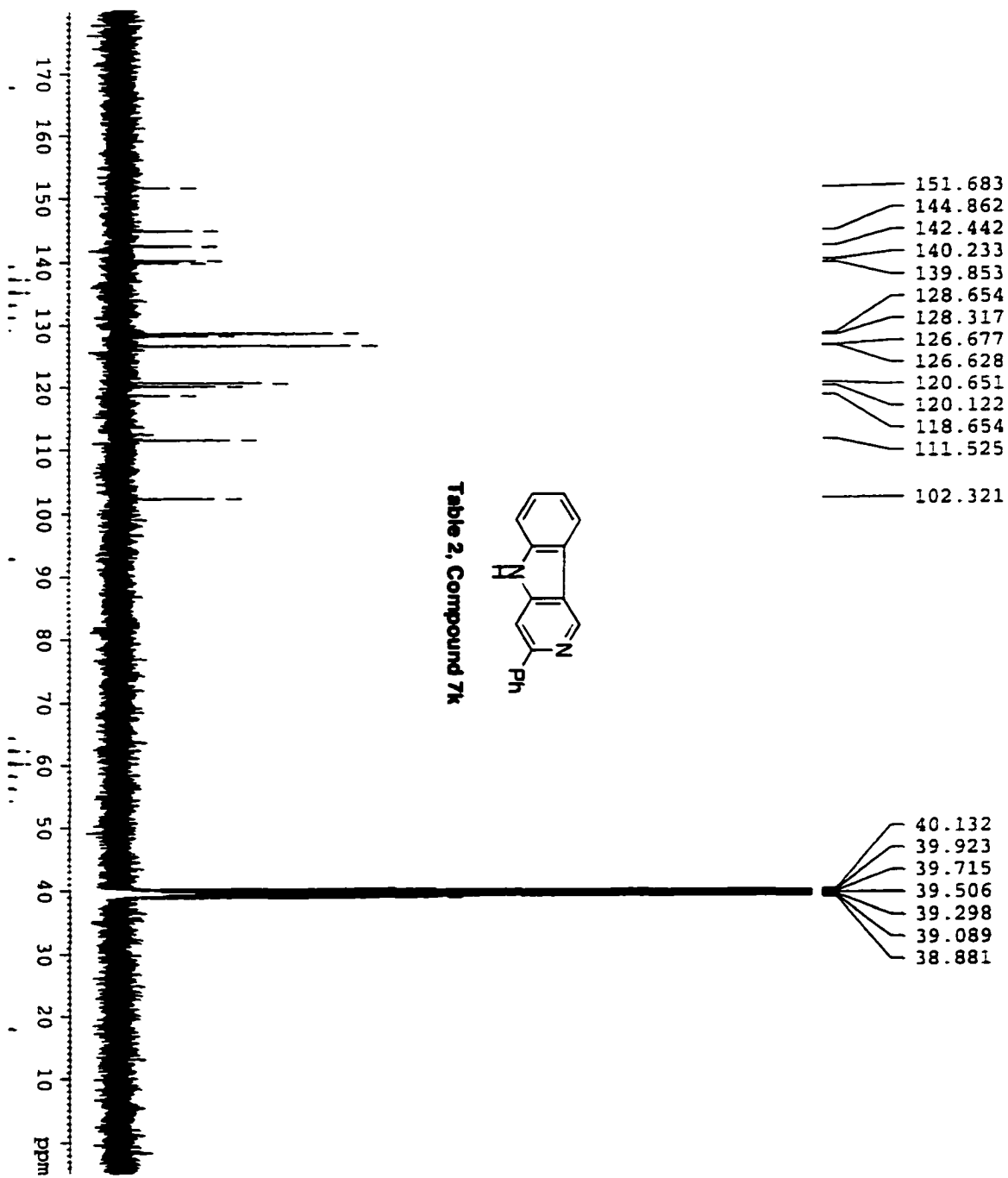




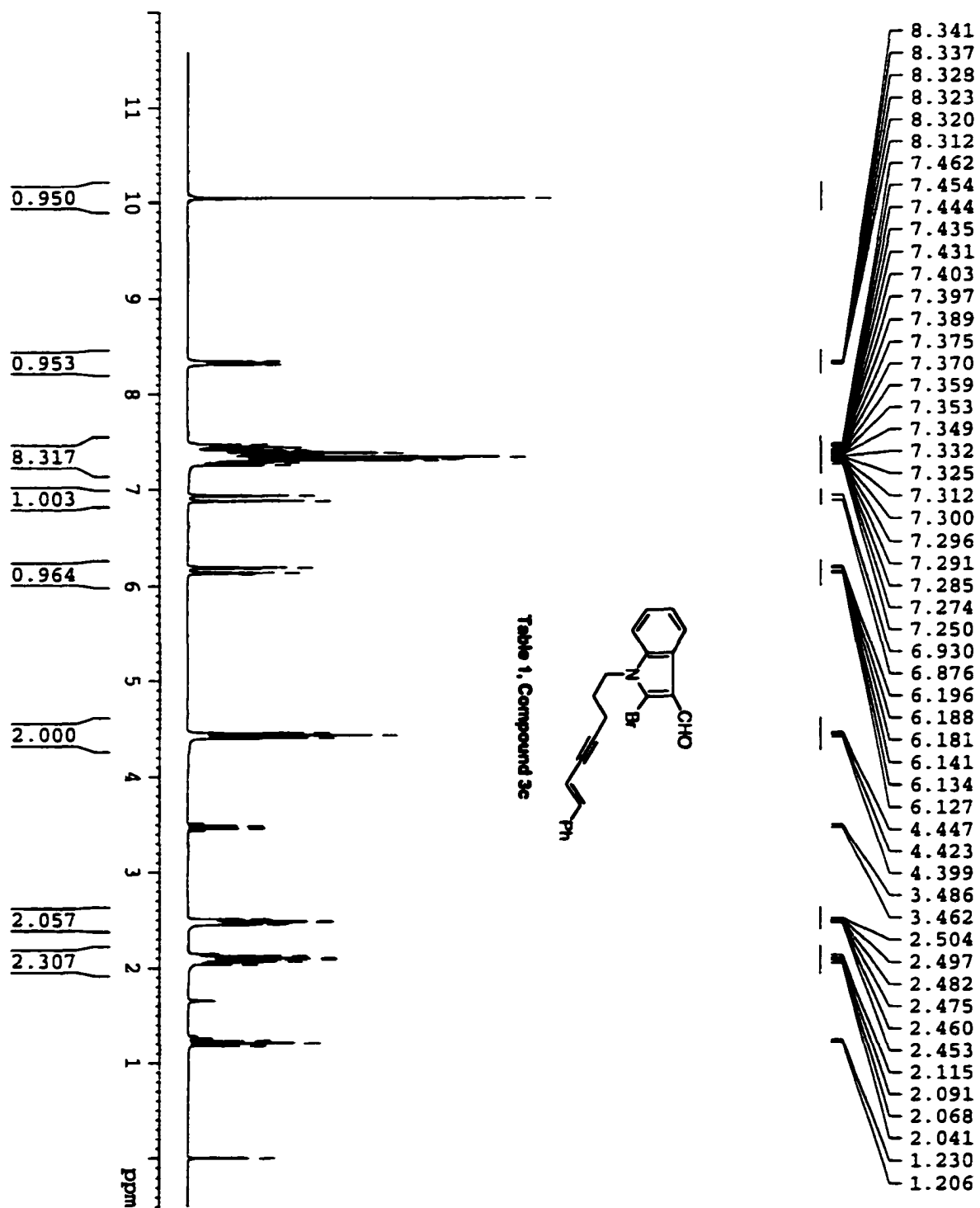


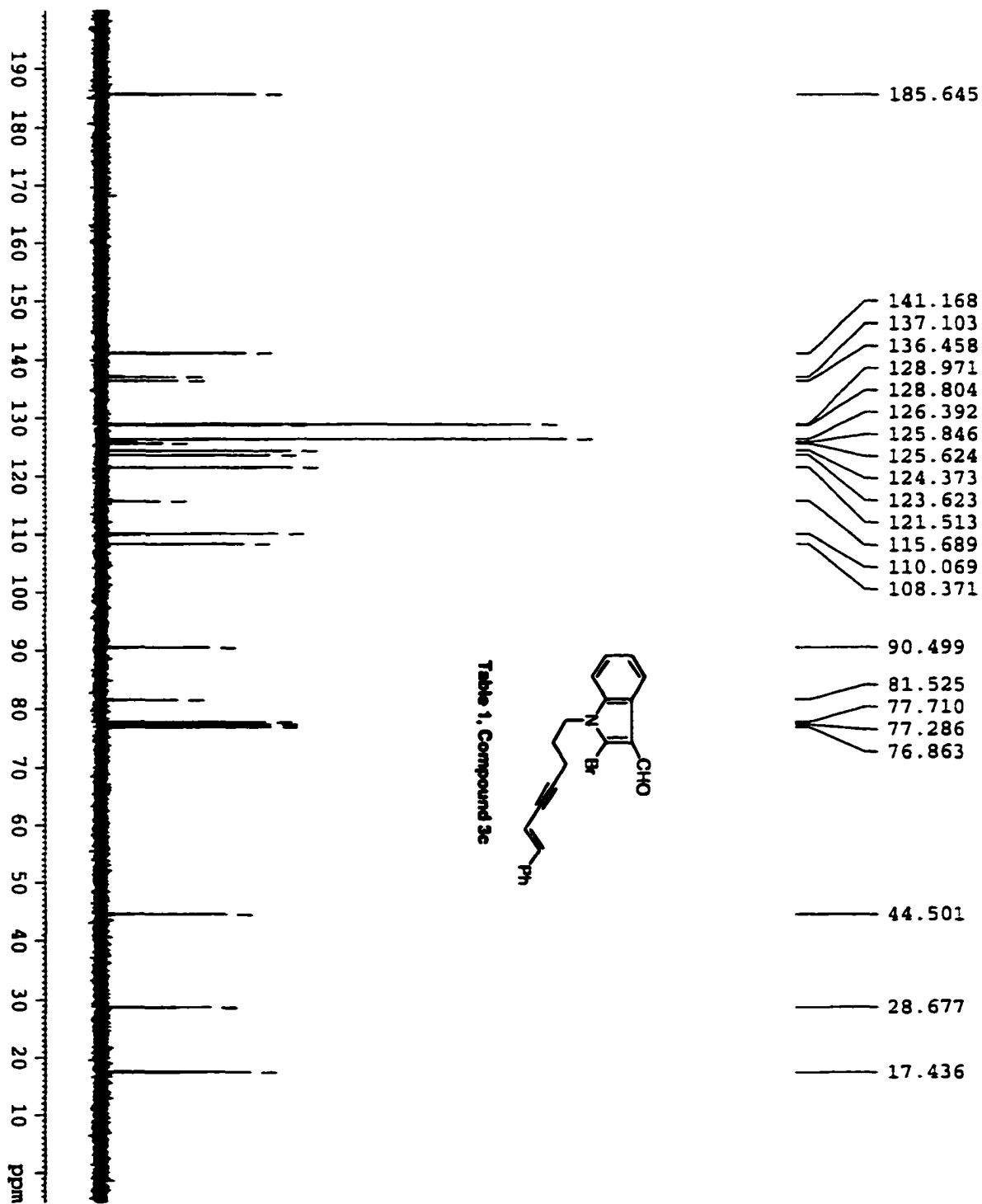


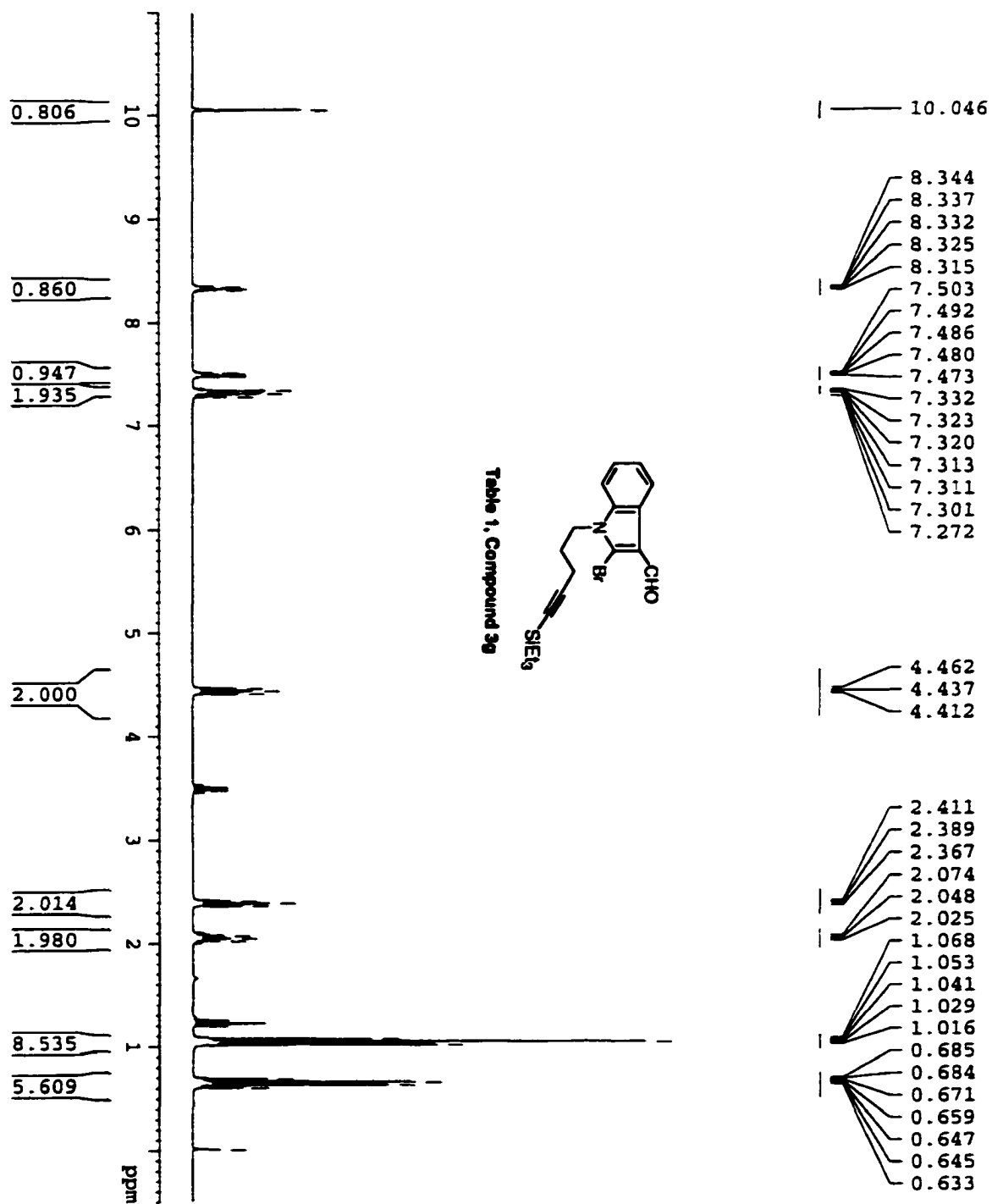


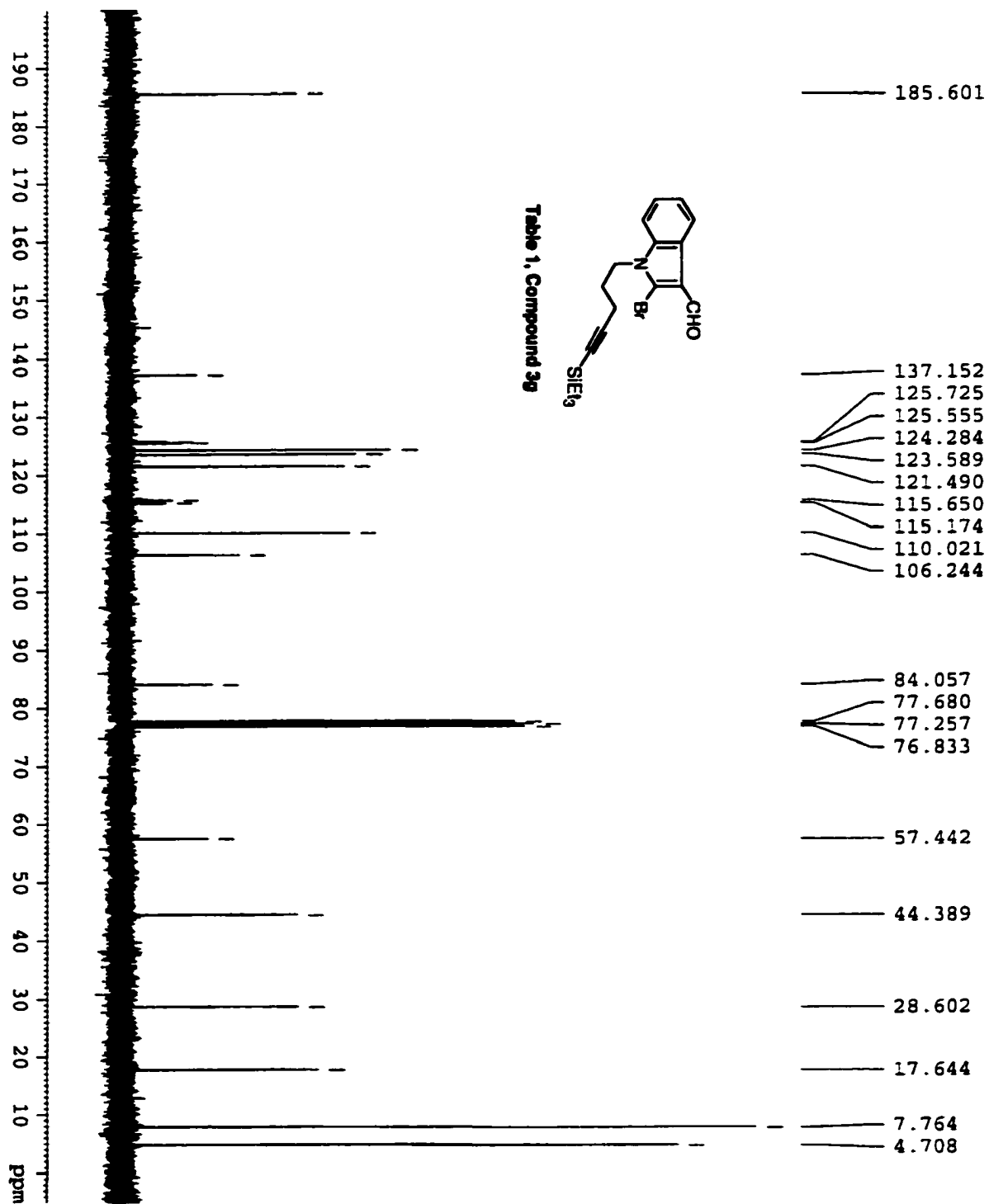


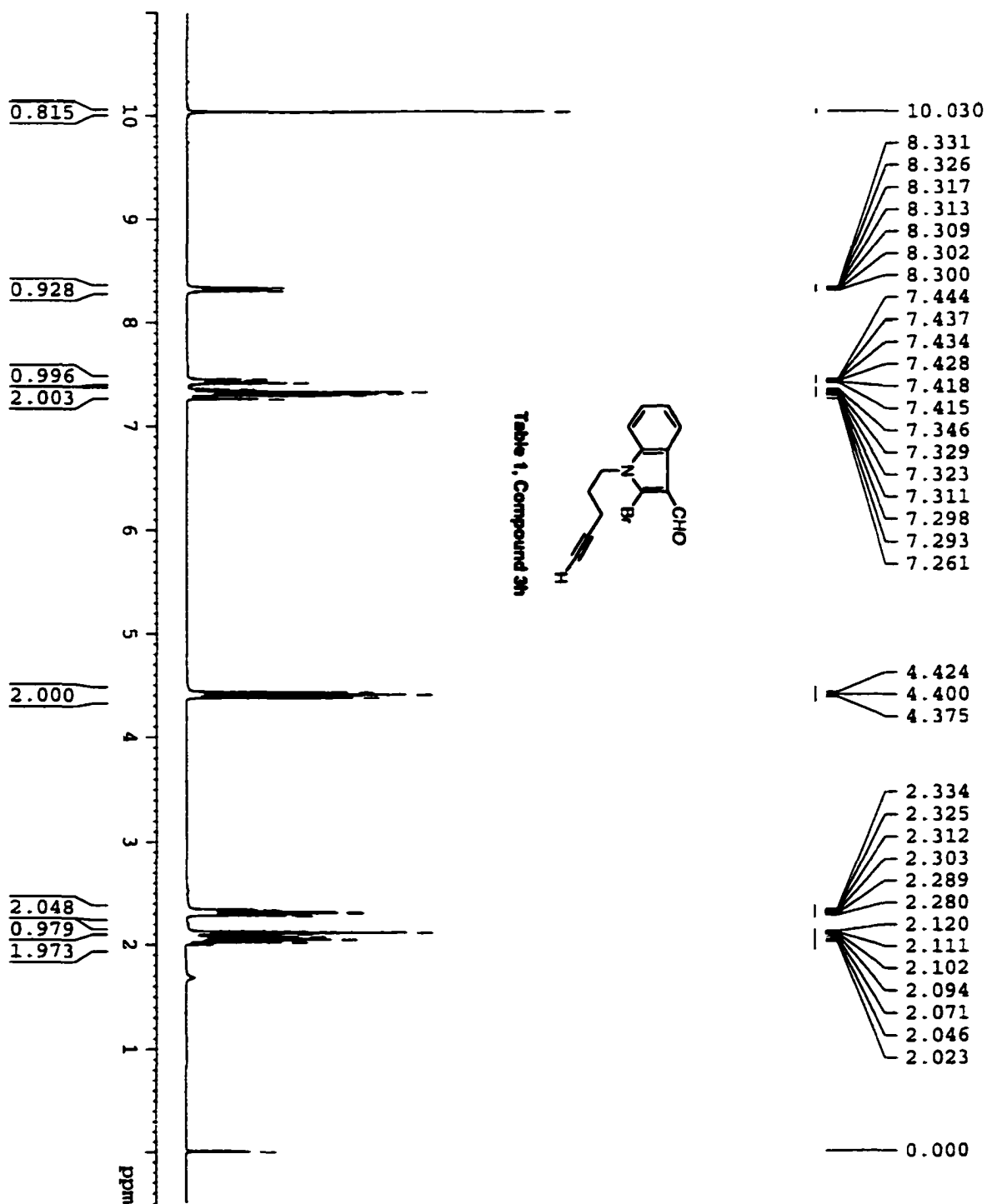
**APPENDIX C. CHAPTER 3  $^1\text{H}$  AND  $^{13}\text{C}$  NMR SPECTRA**













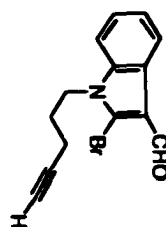
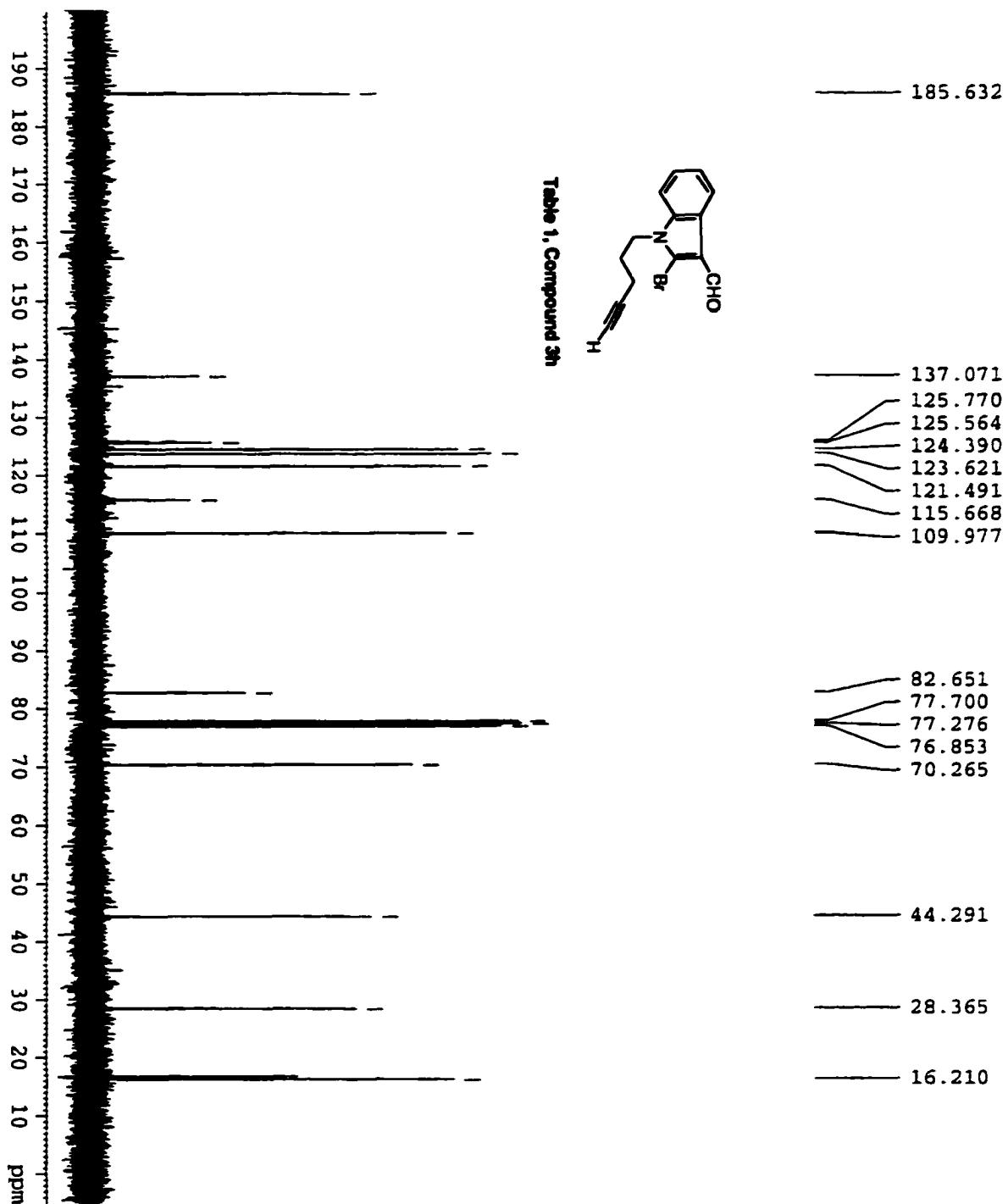
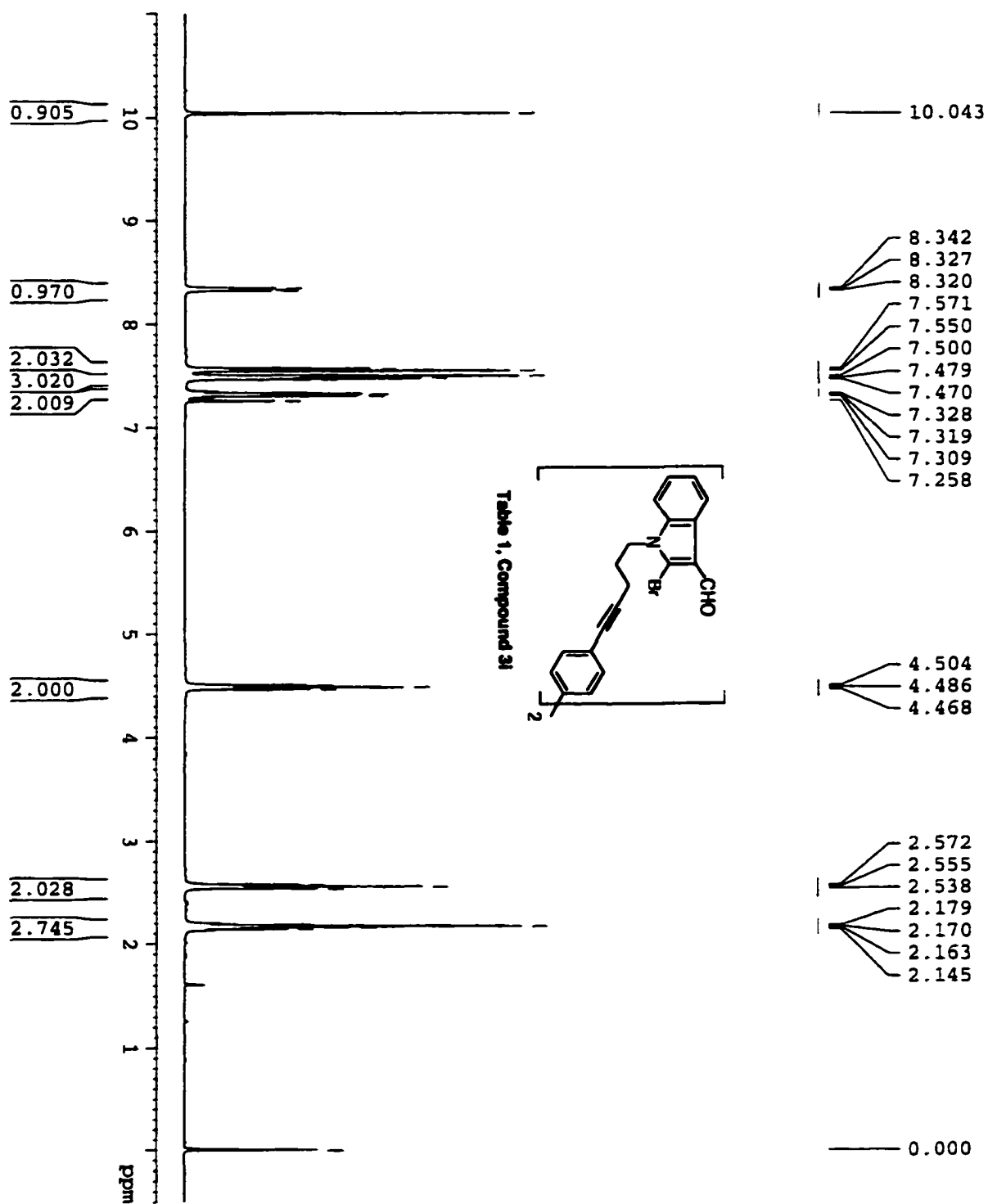
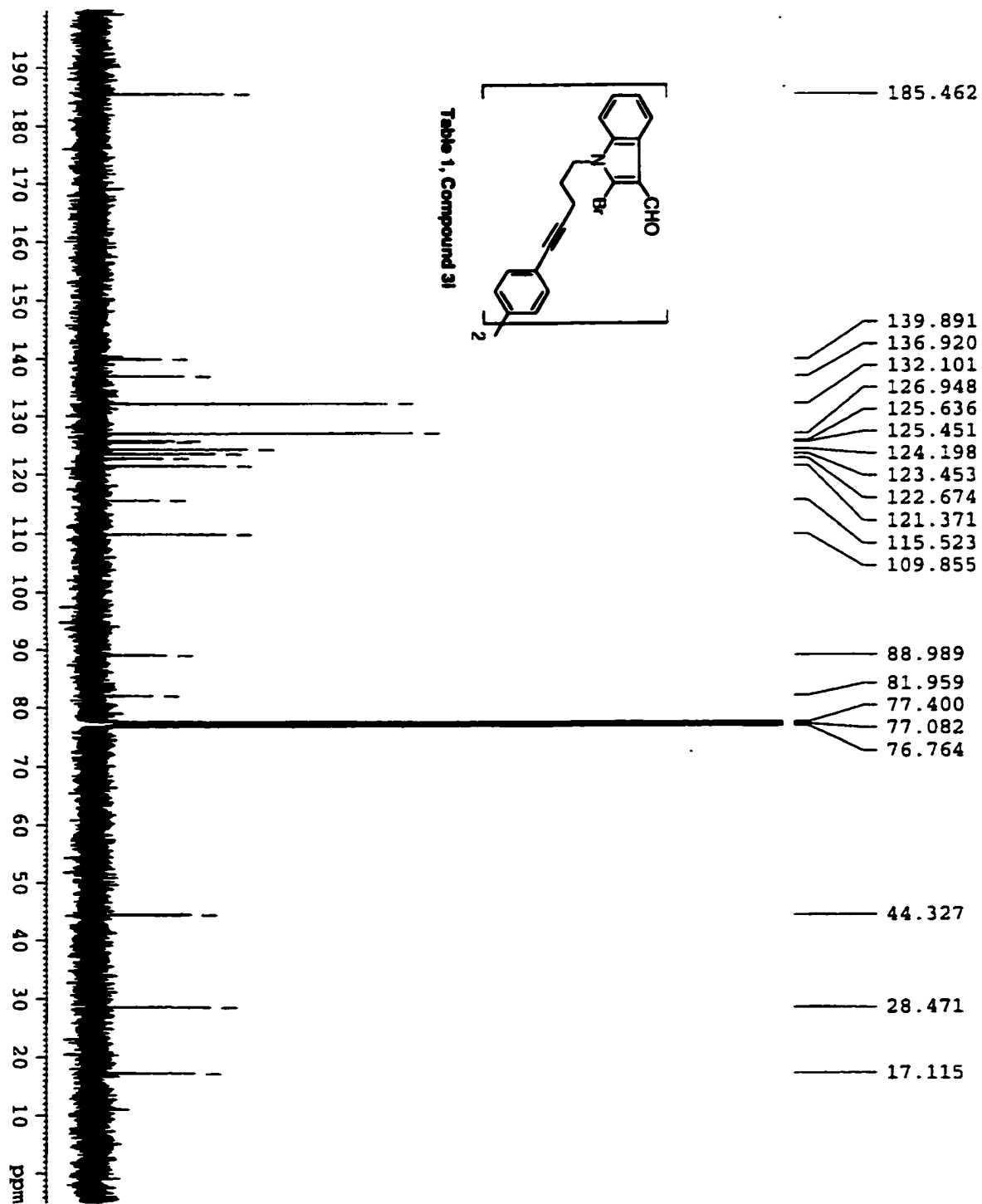
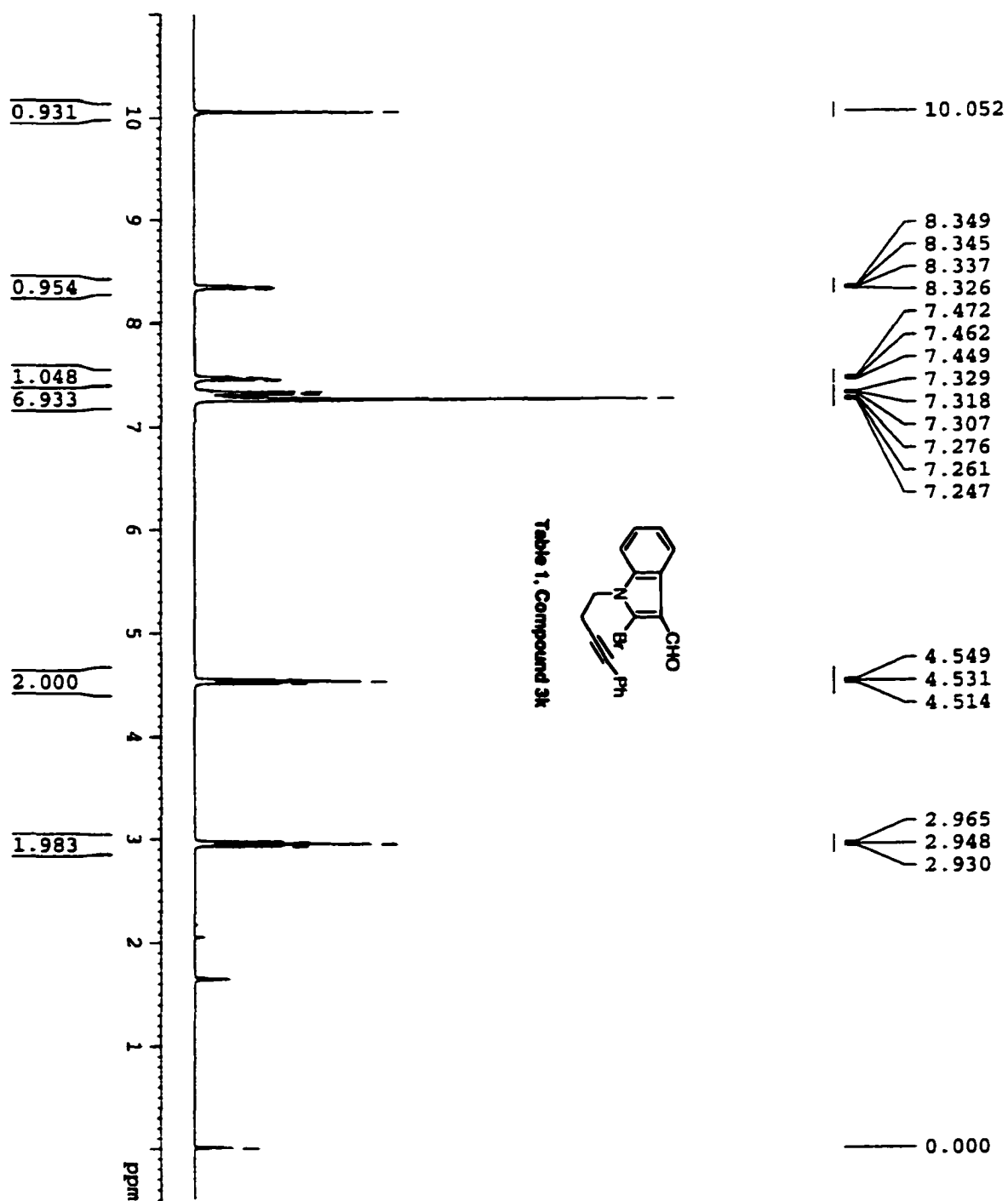


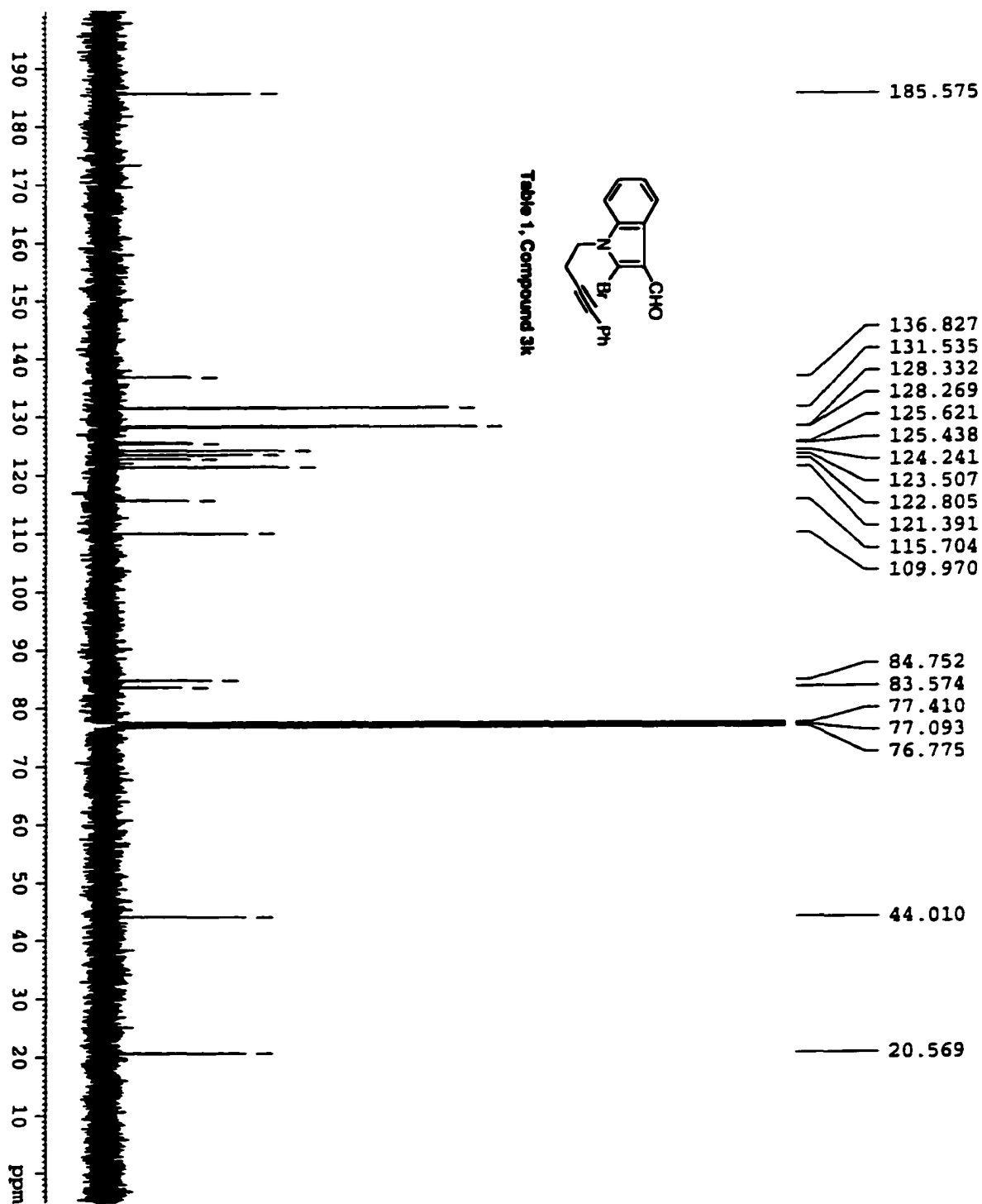
Table 1, Compound 3h

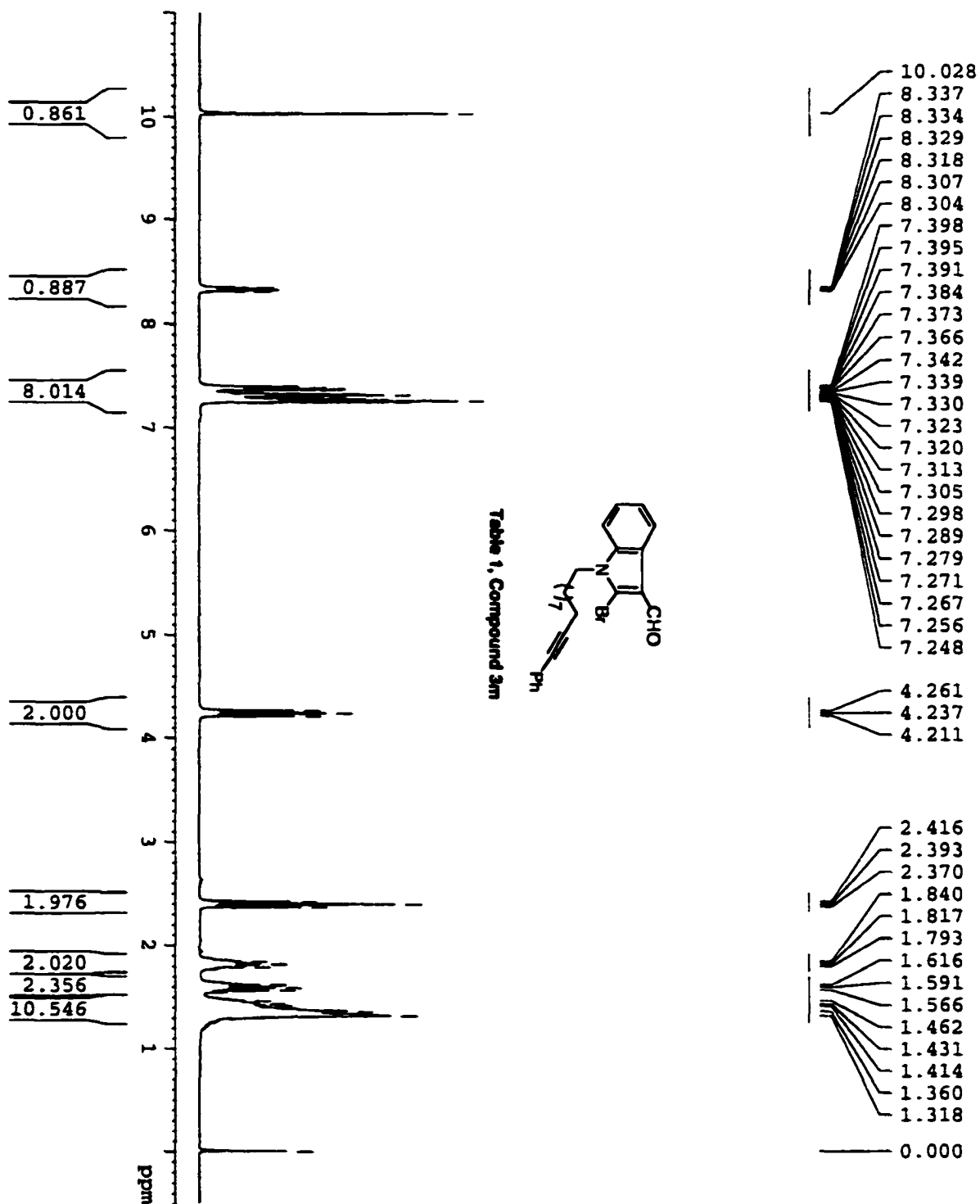


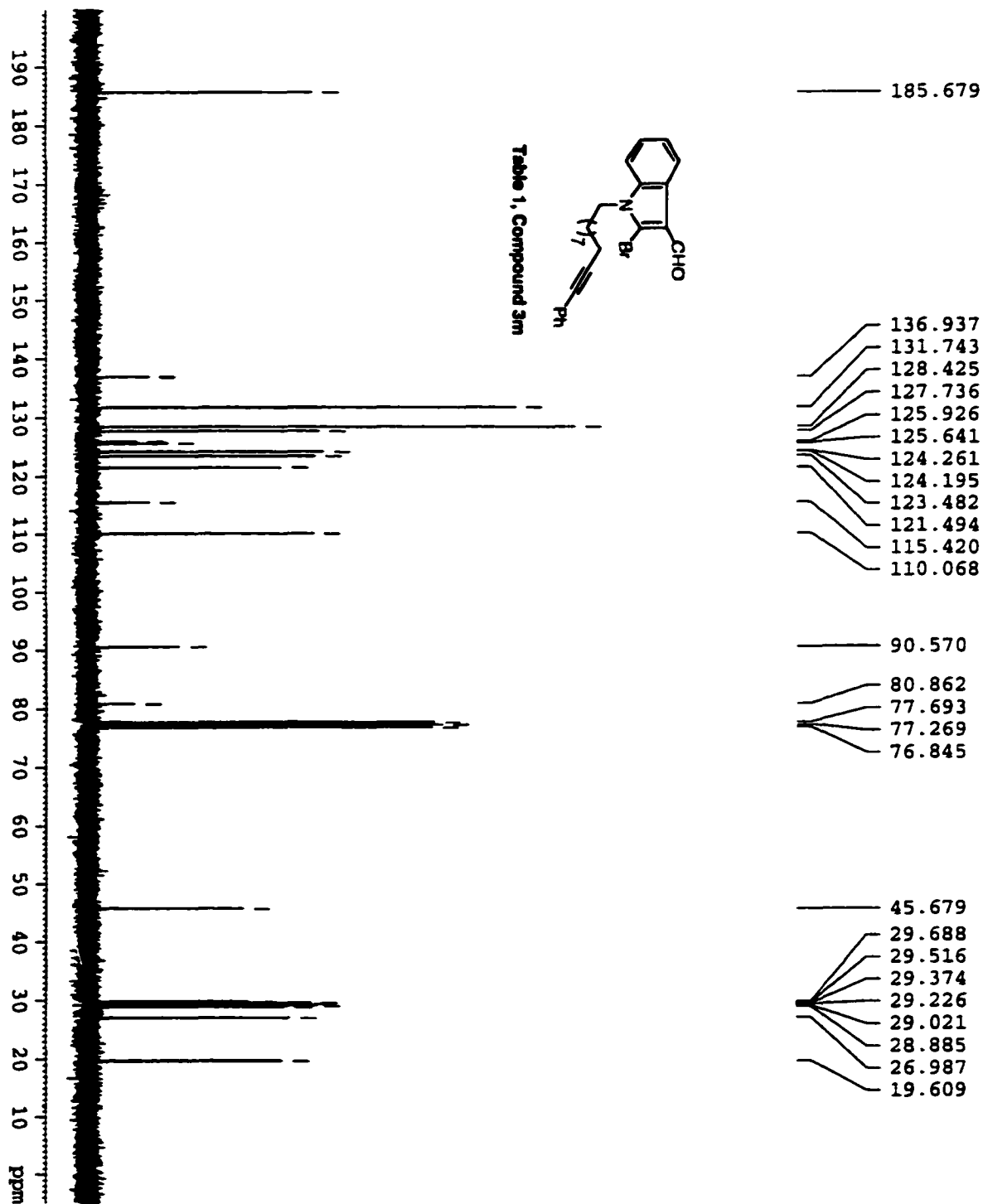


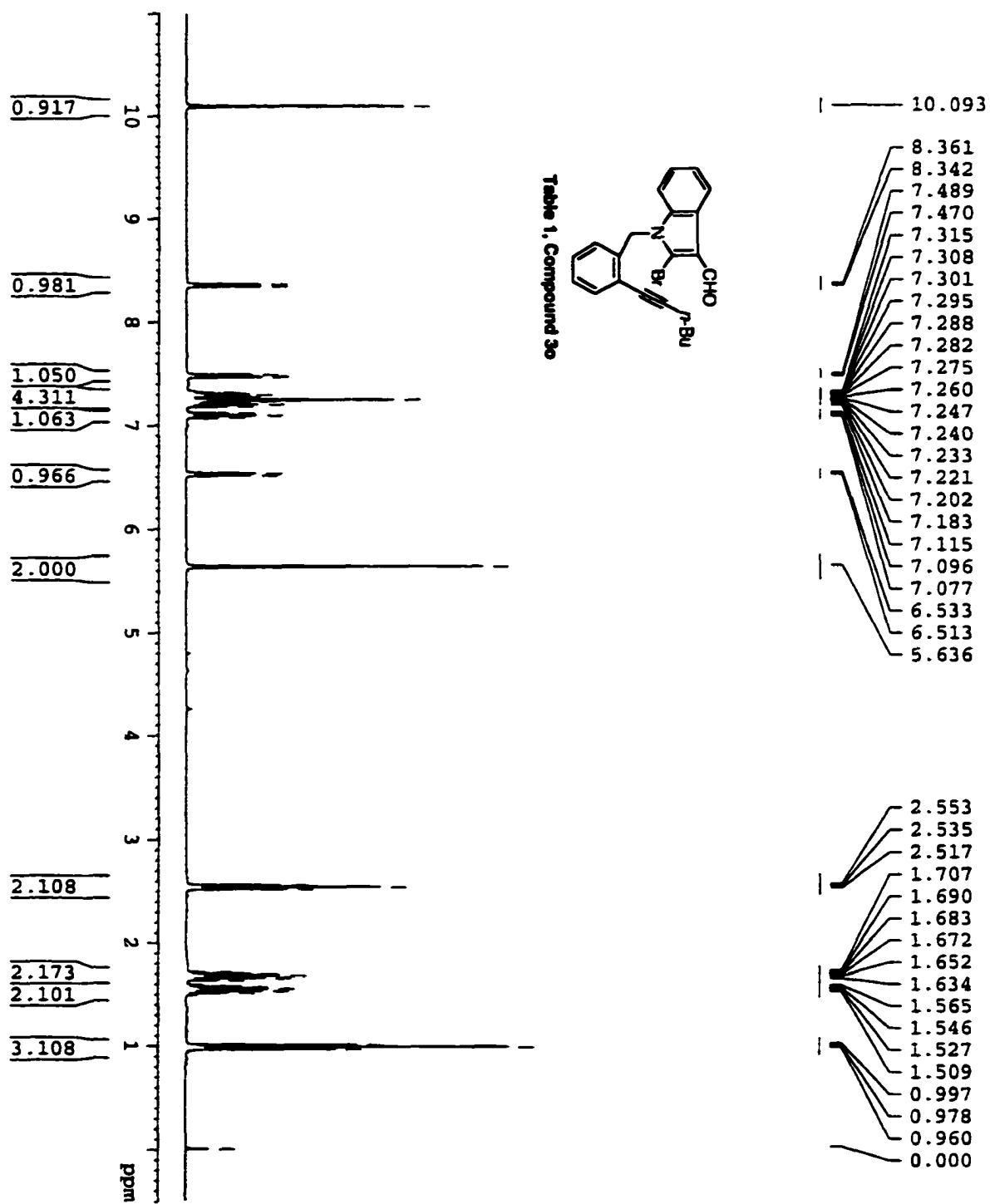




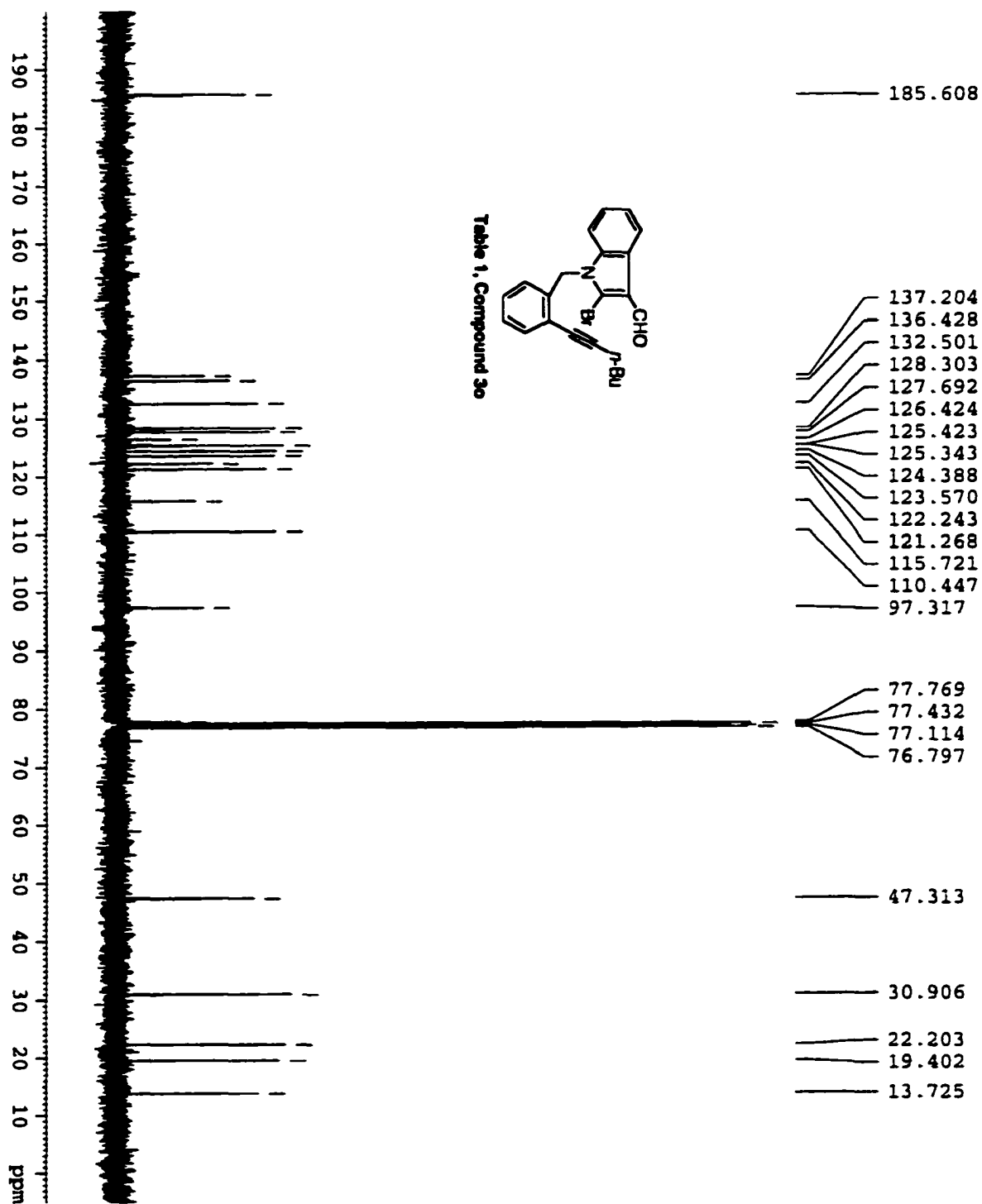


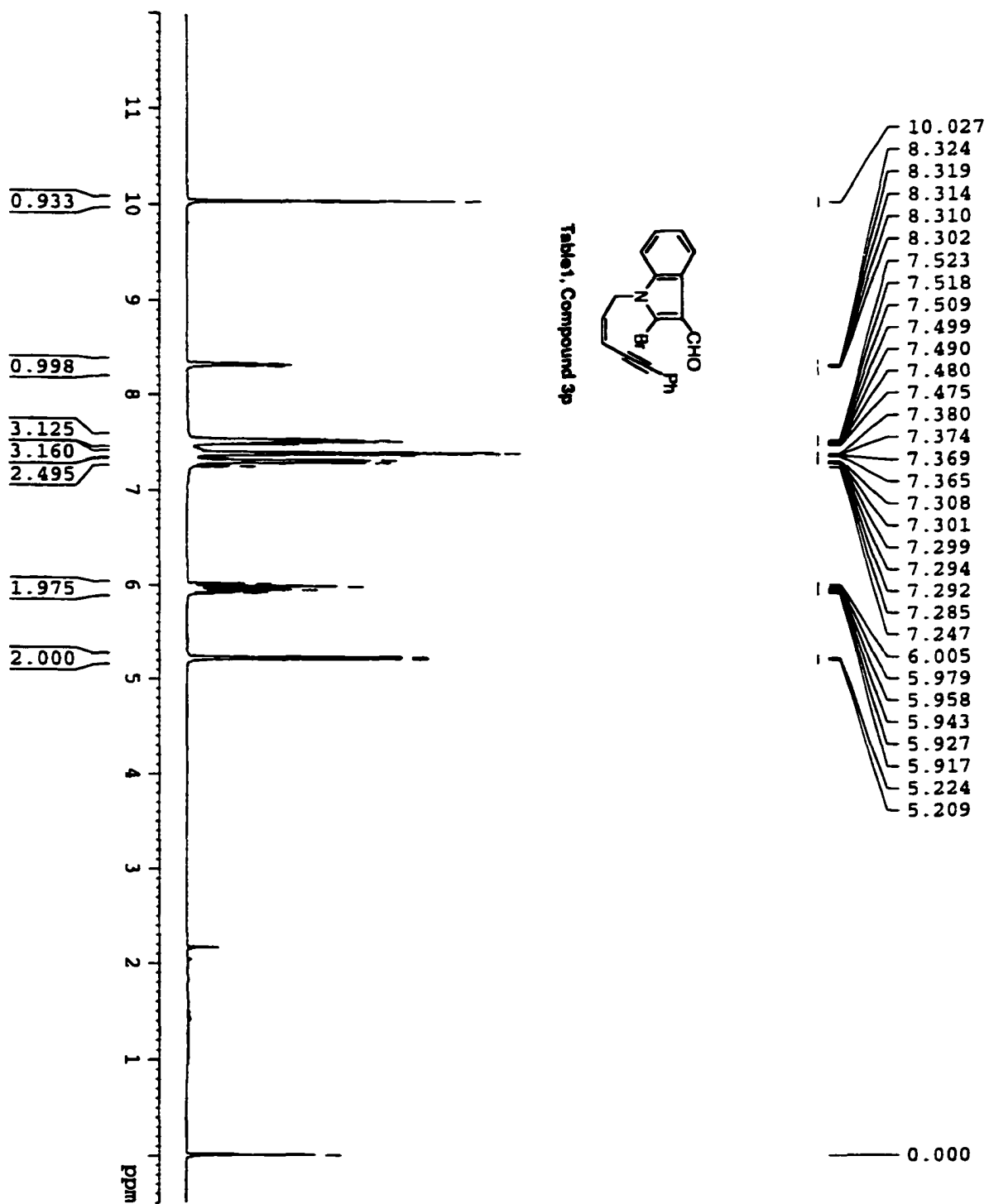












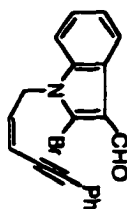
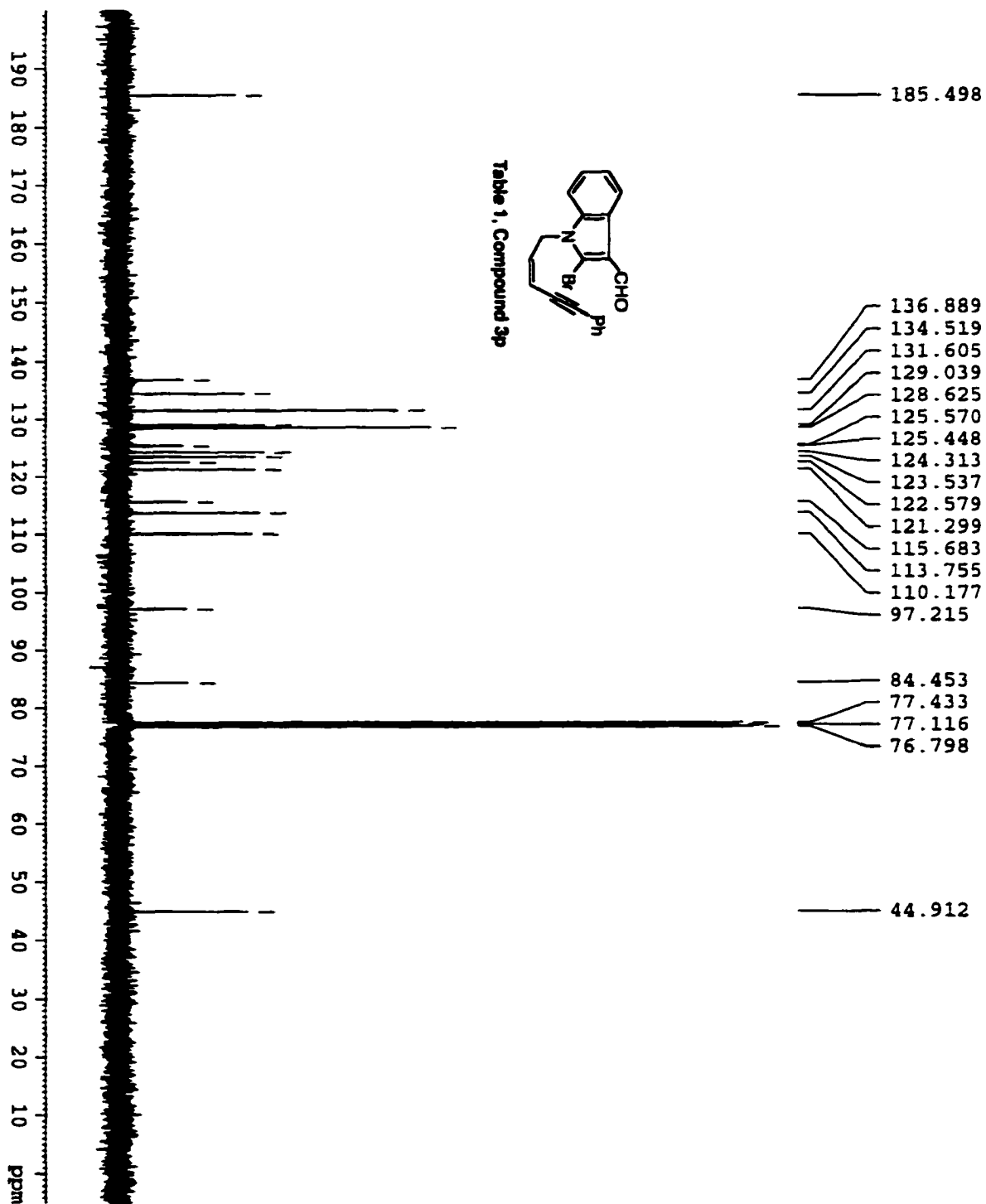
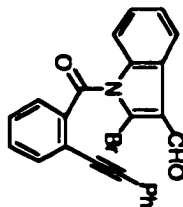
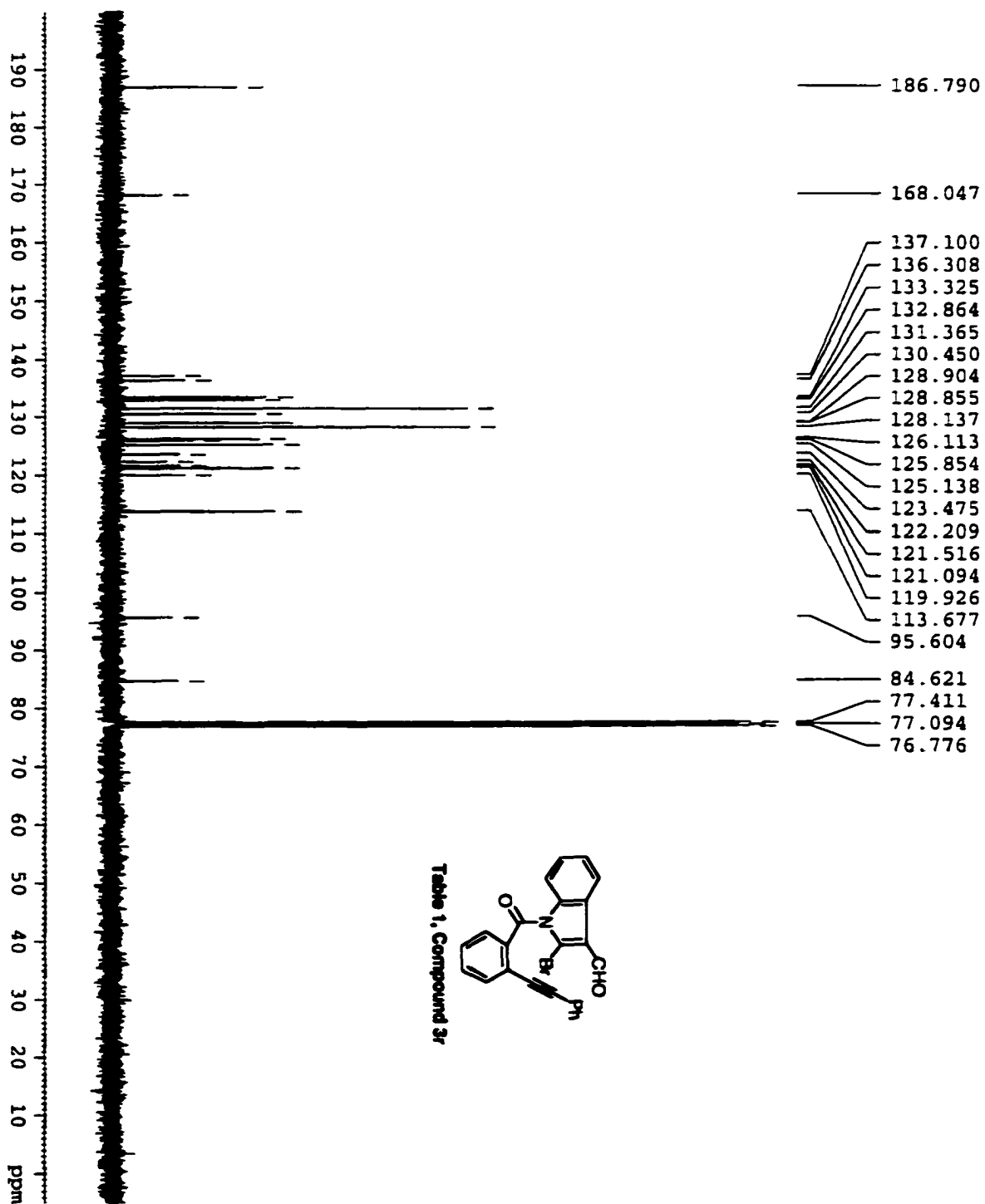
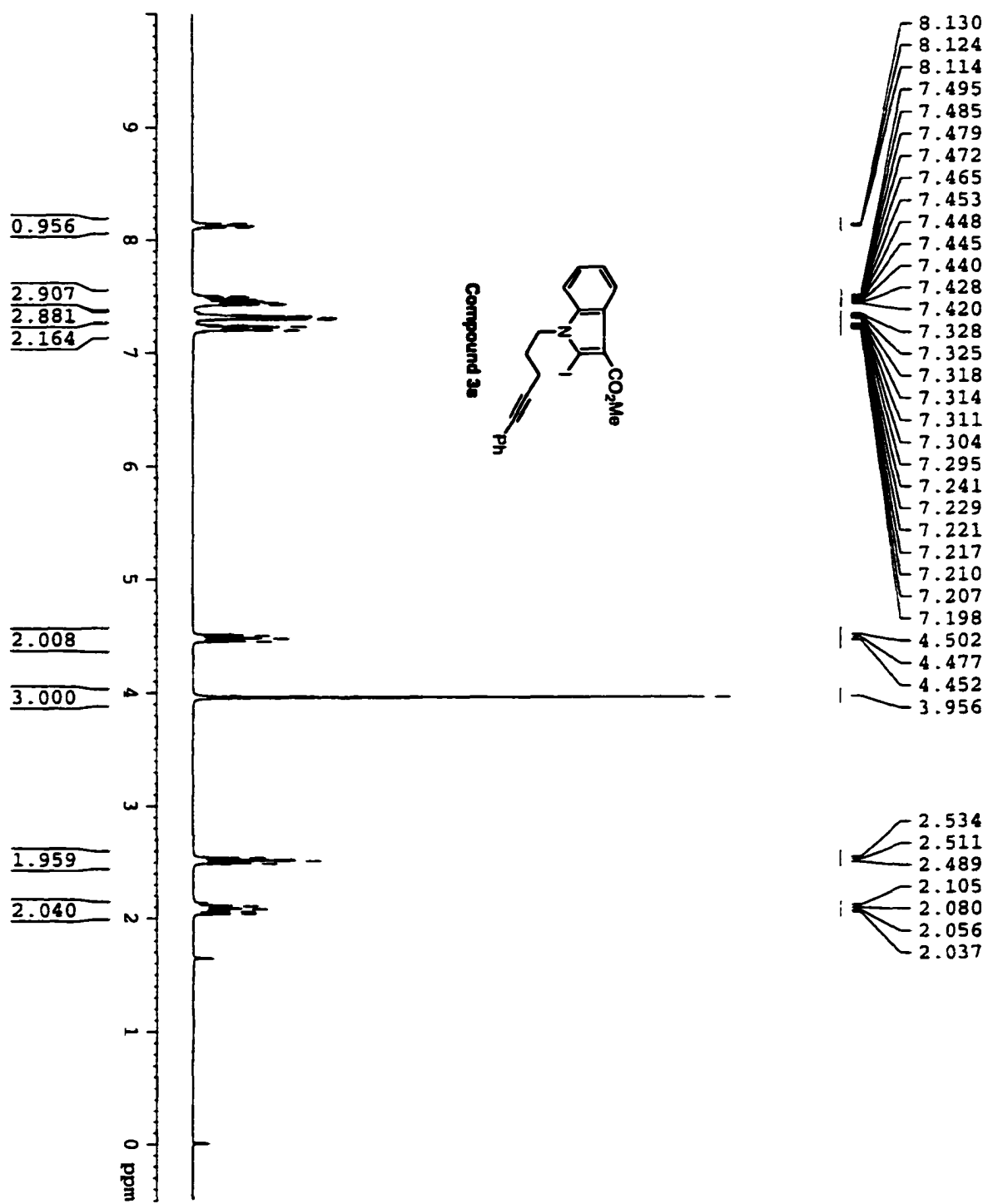


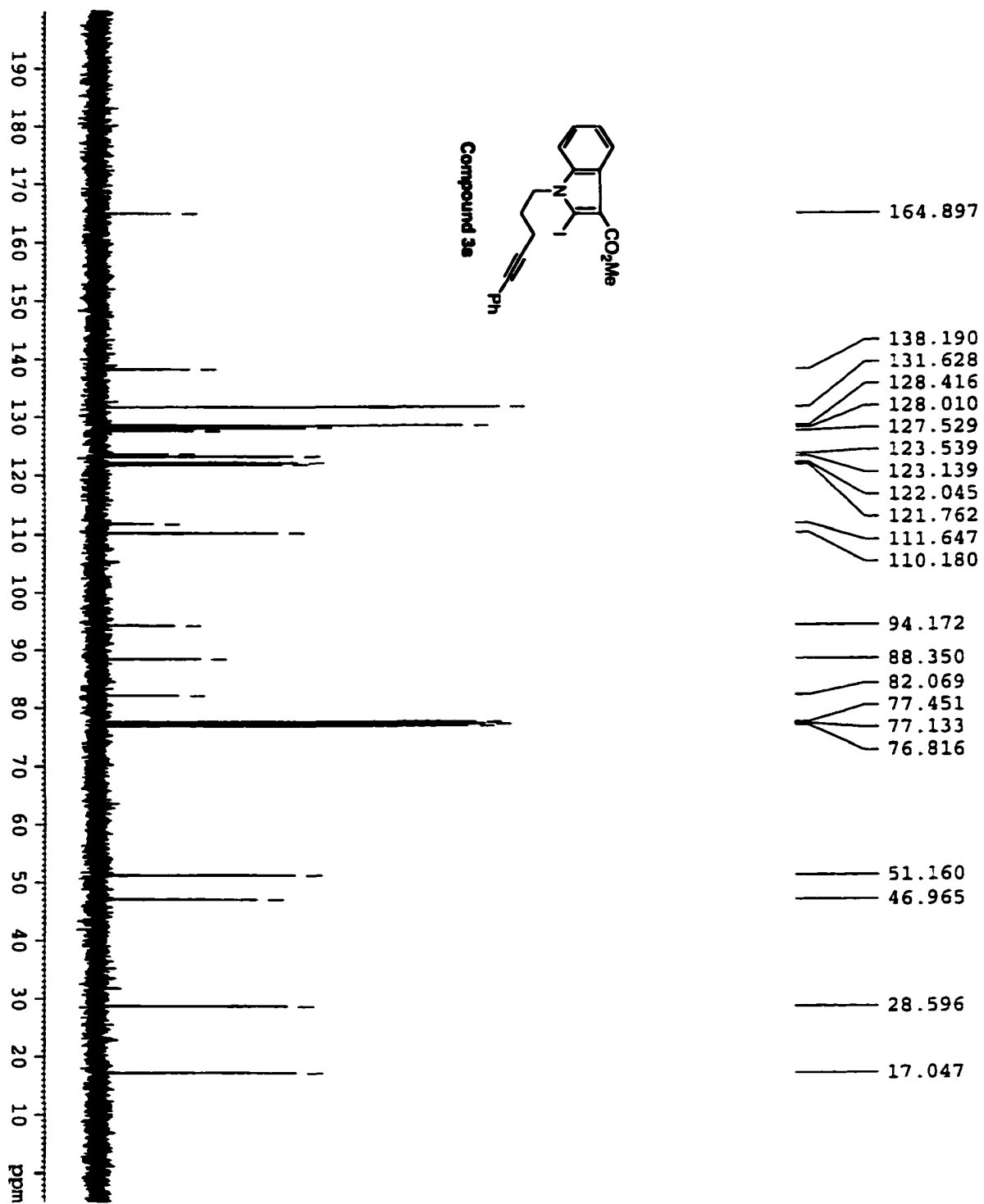
Table 1. Compound 3p

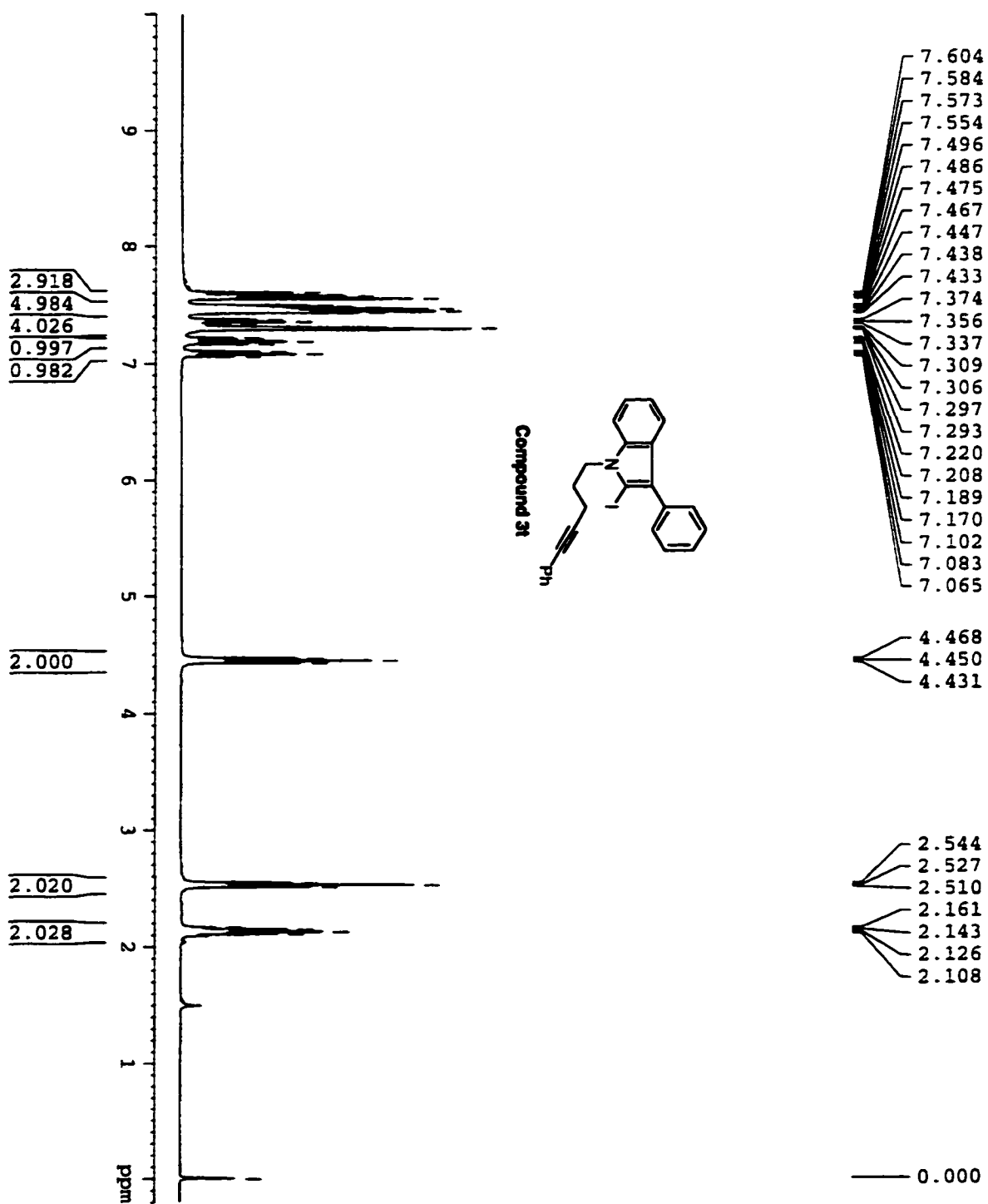




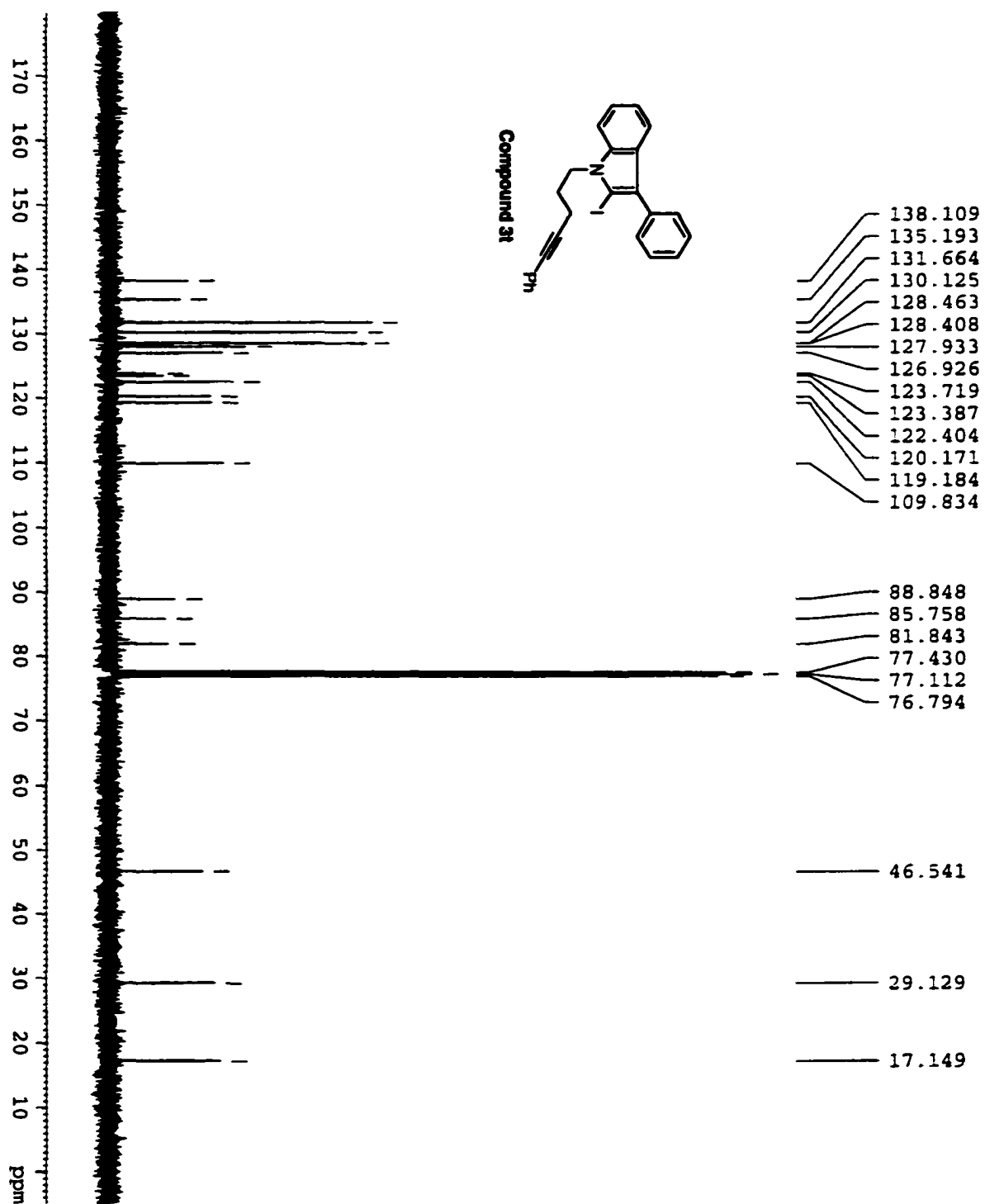


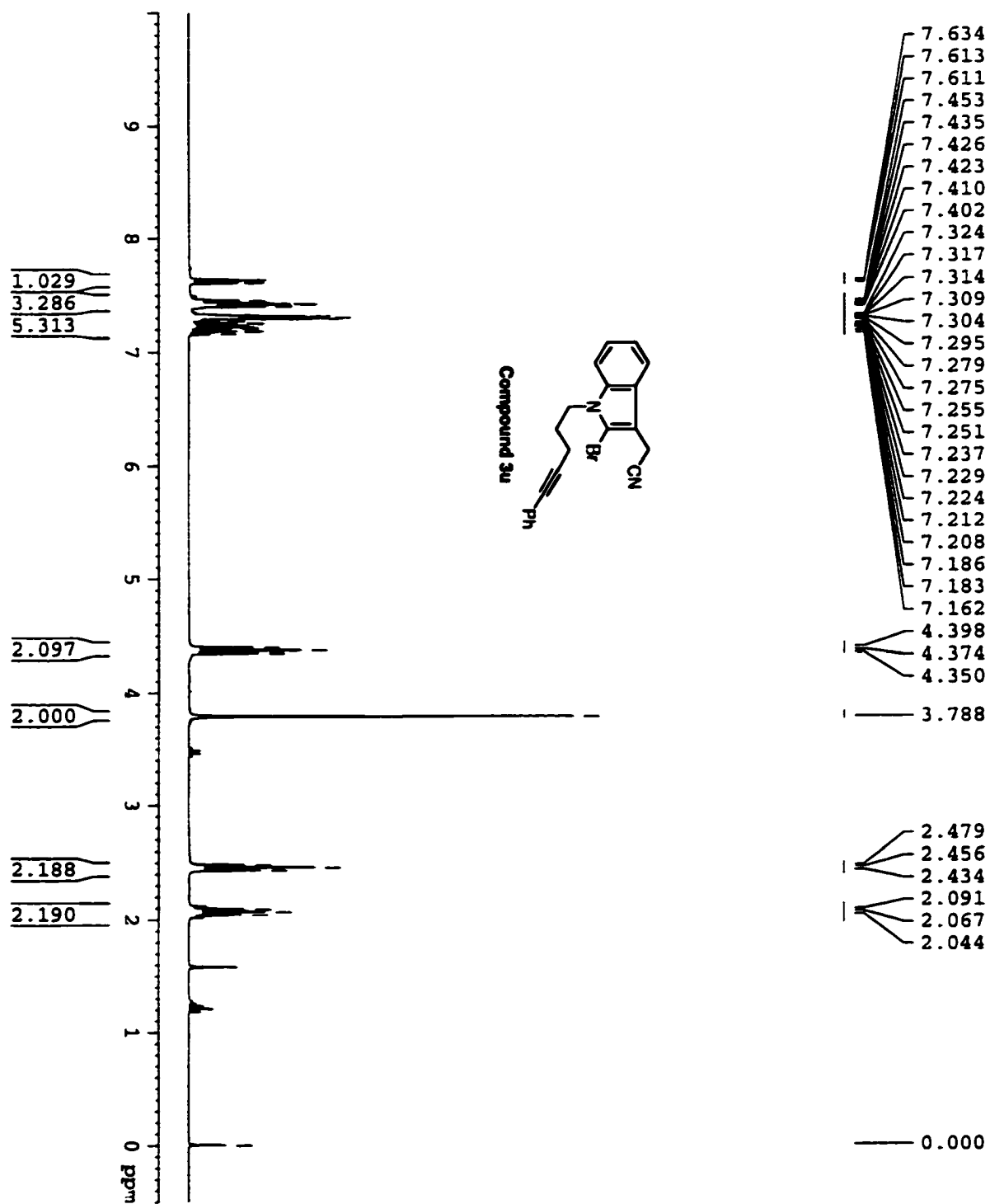


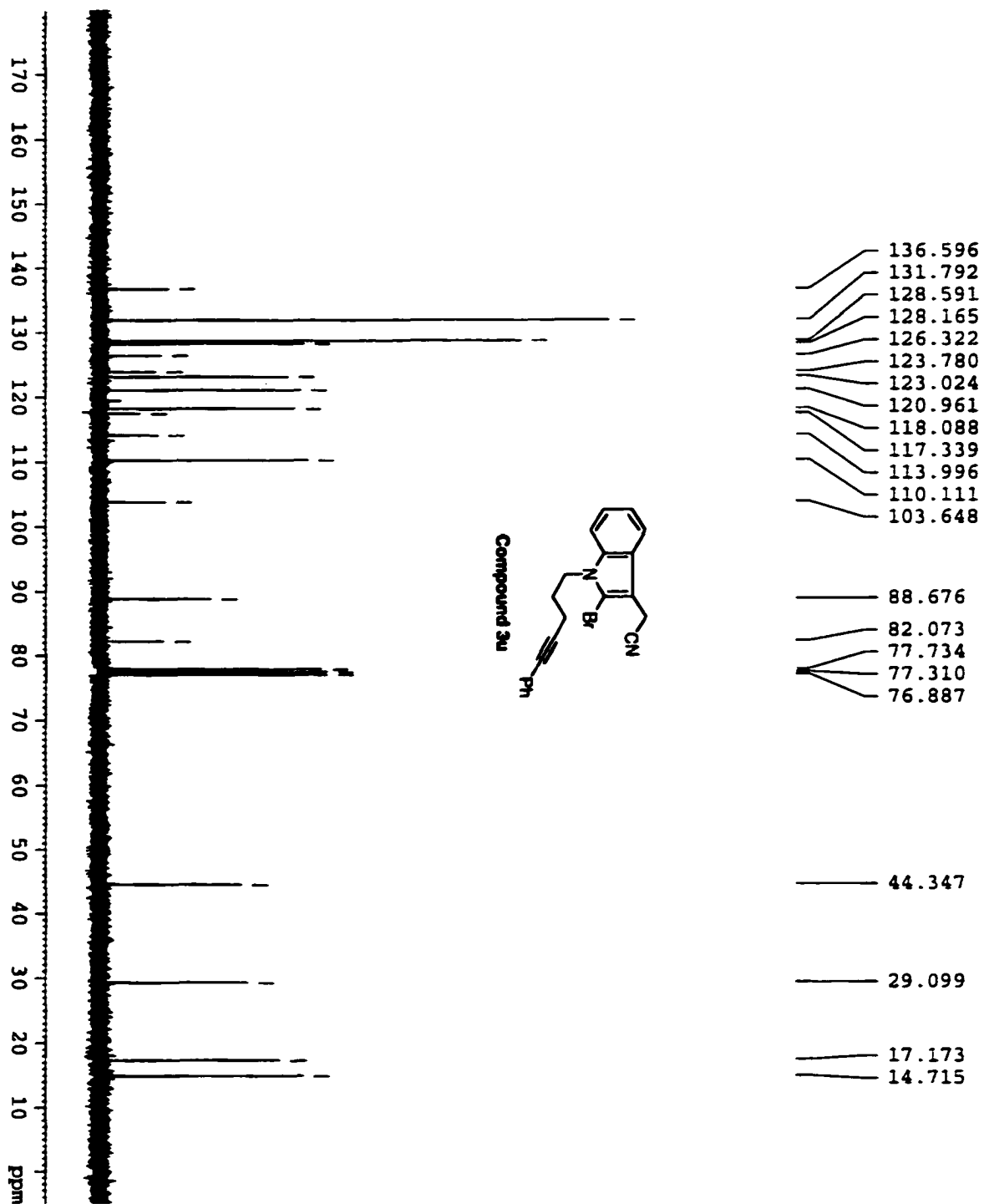


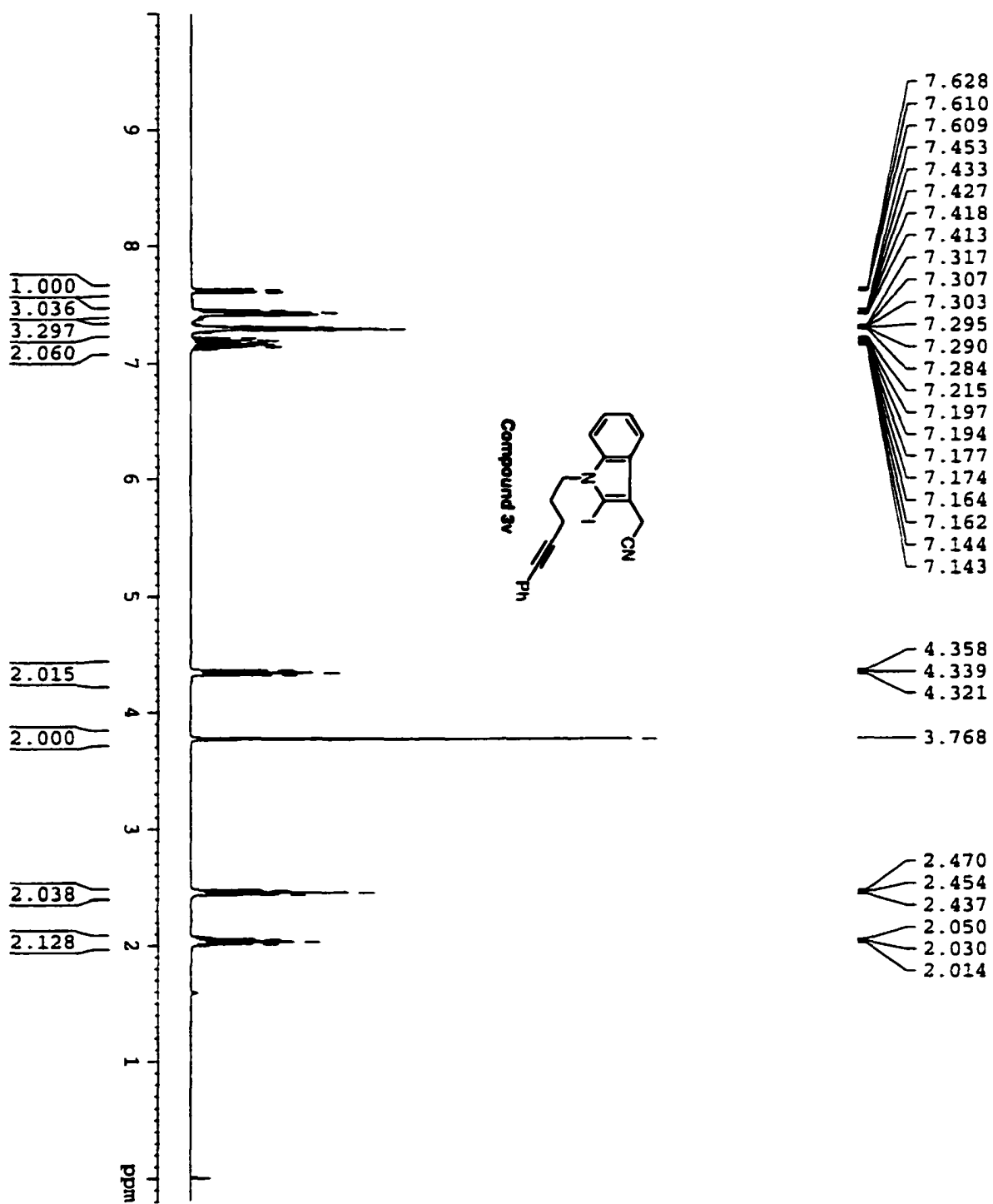


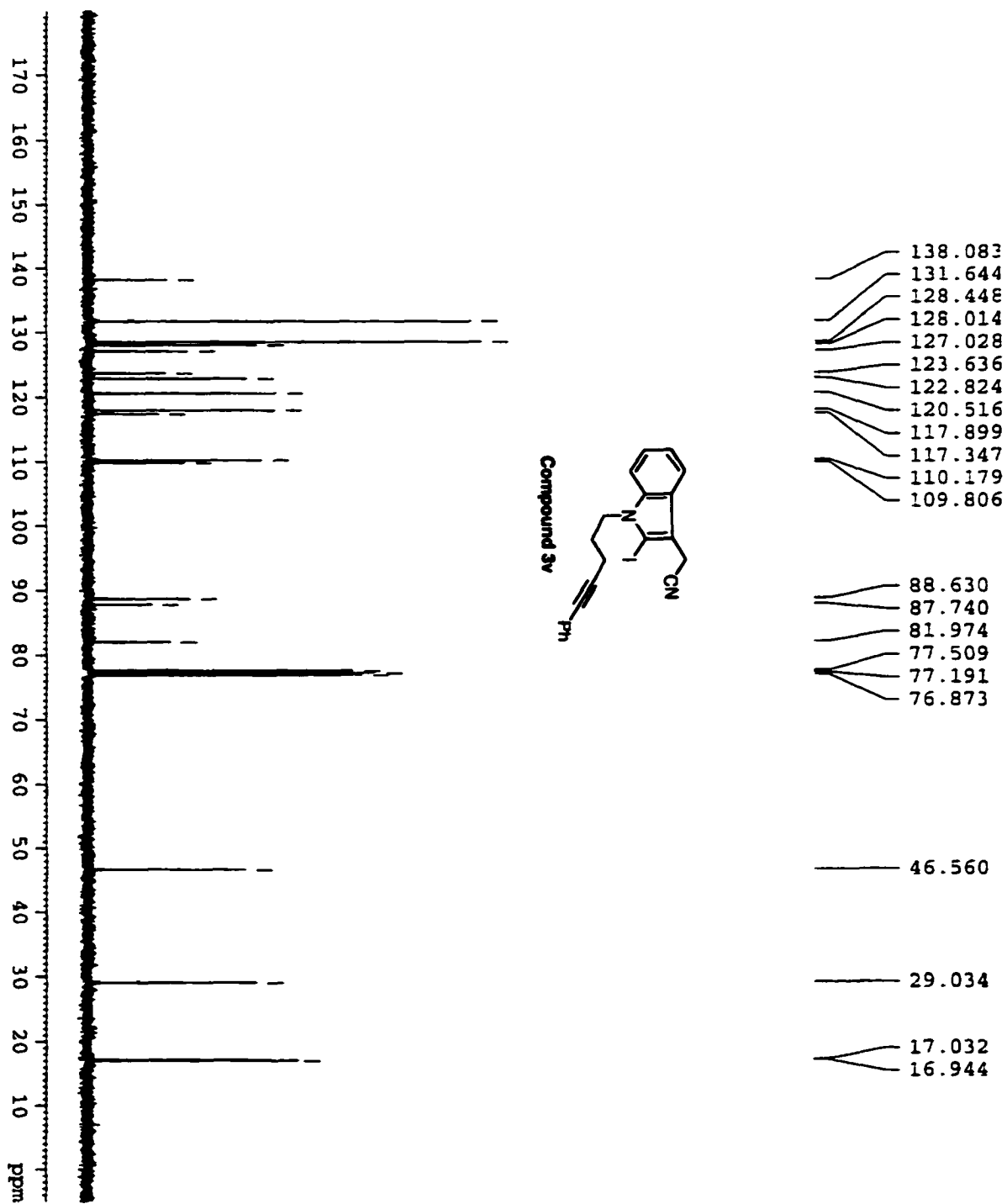


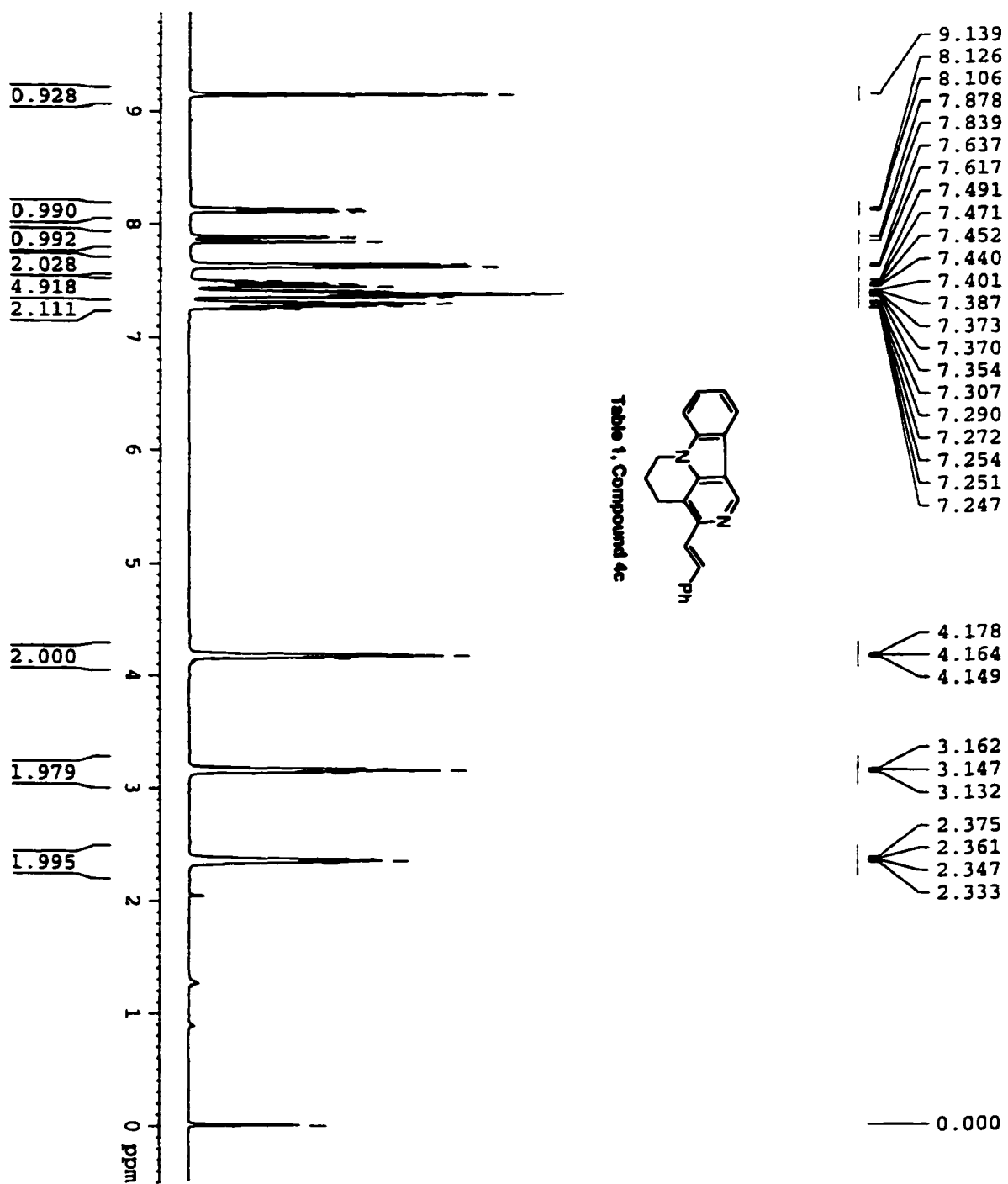


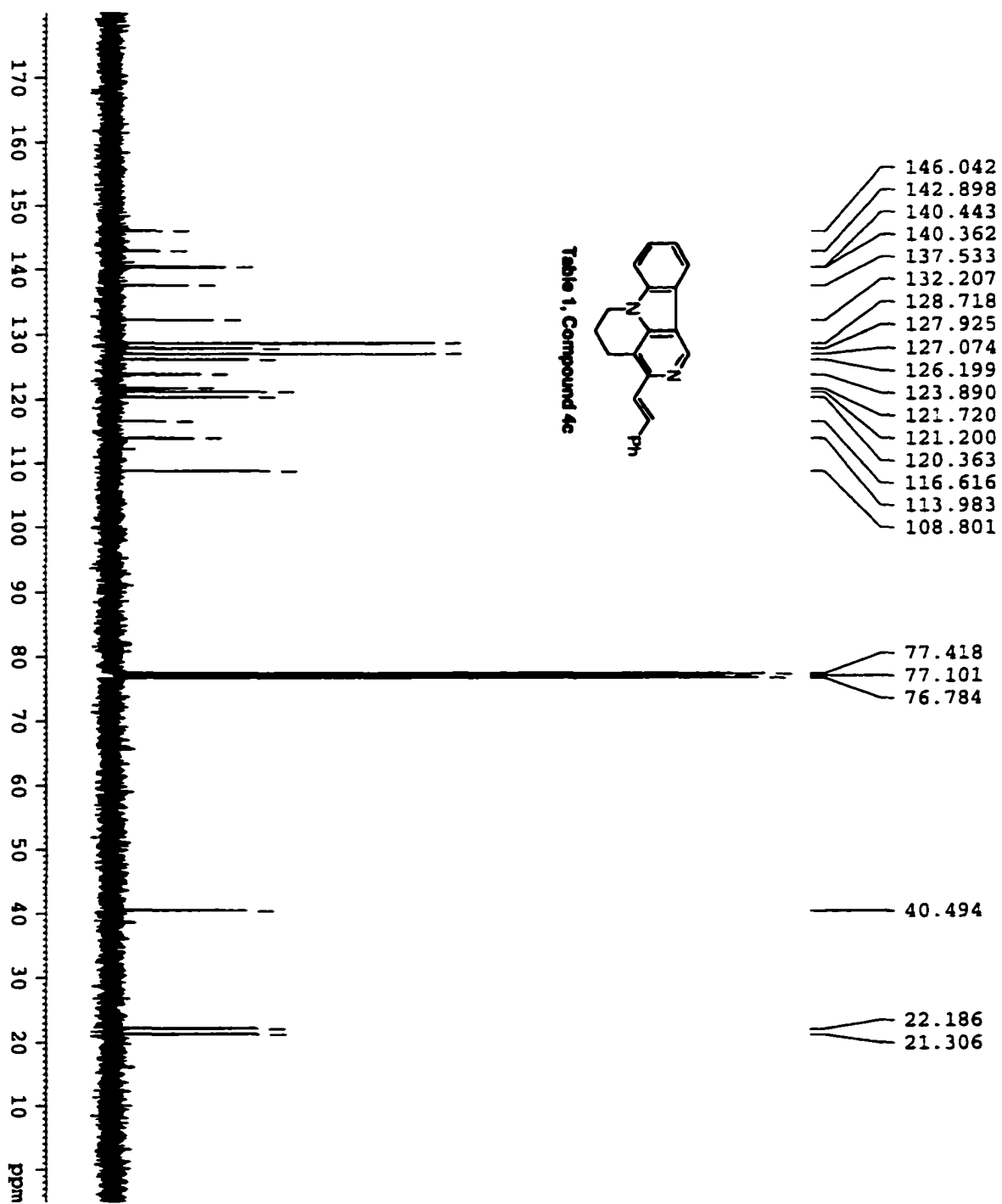


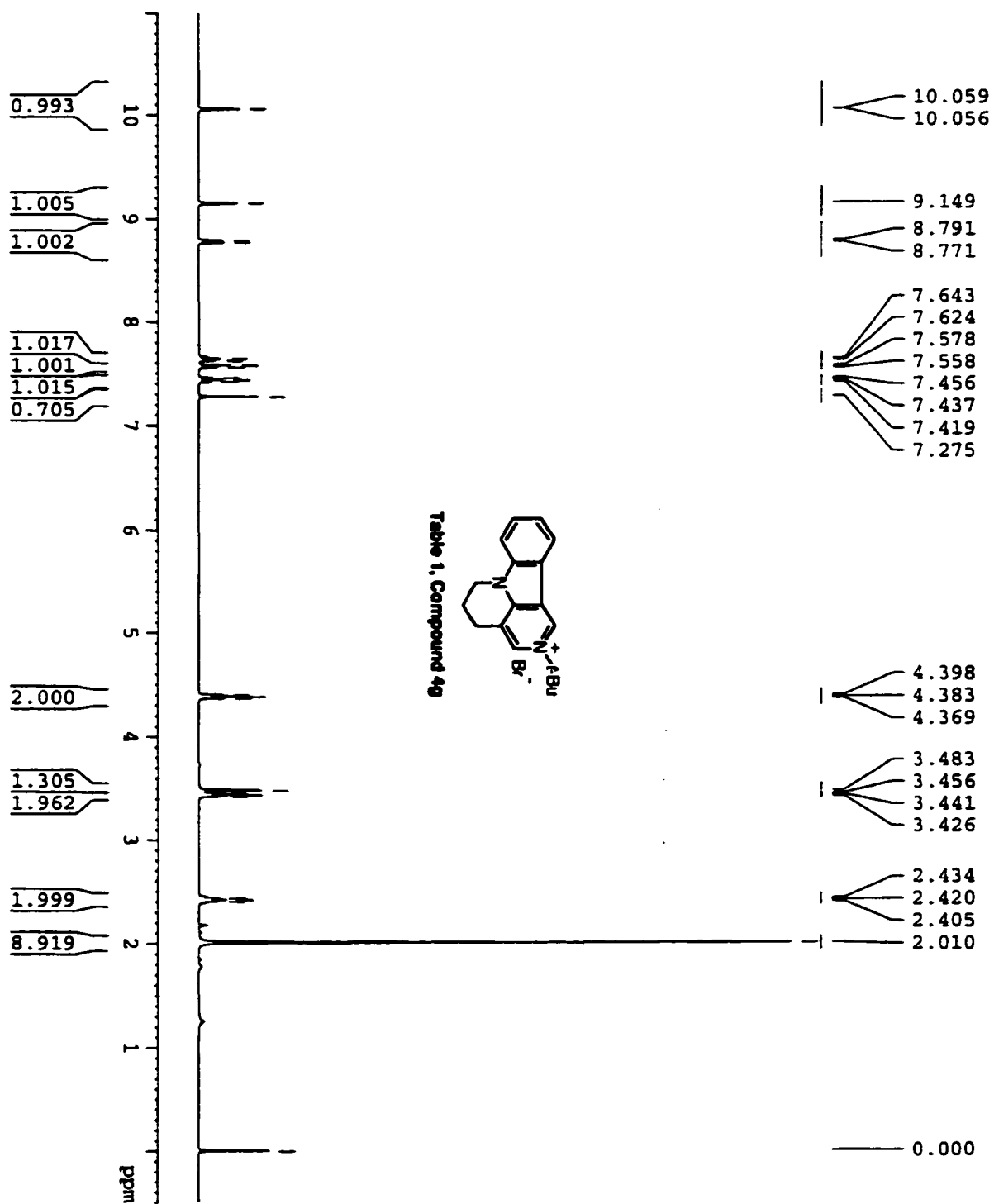




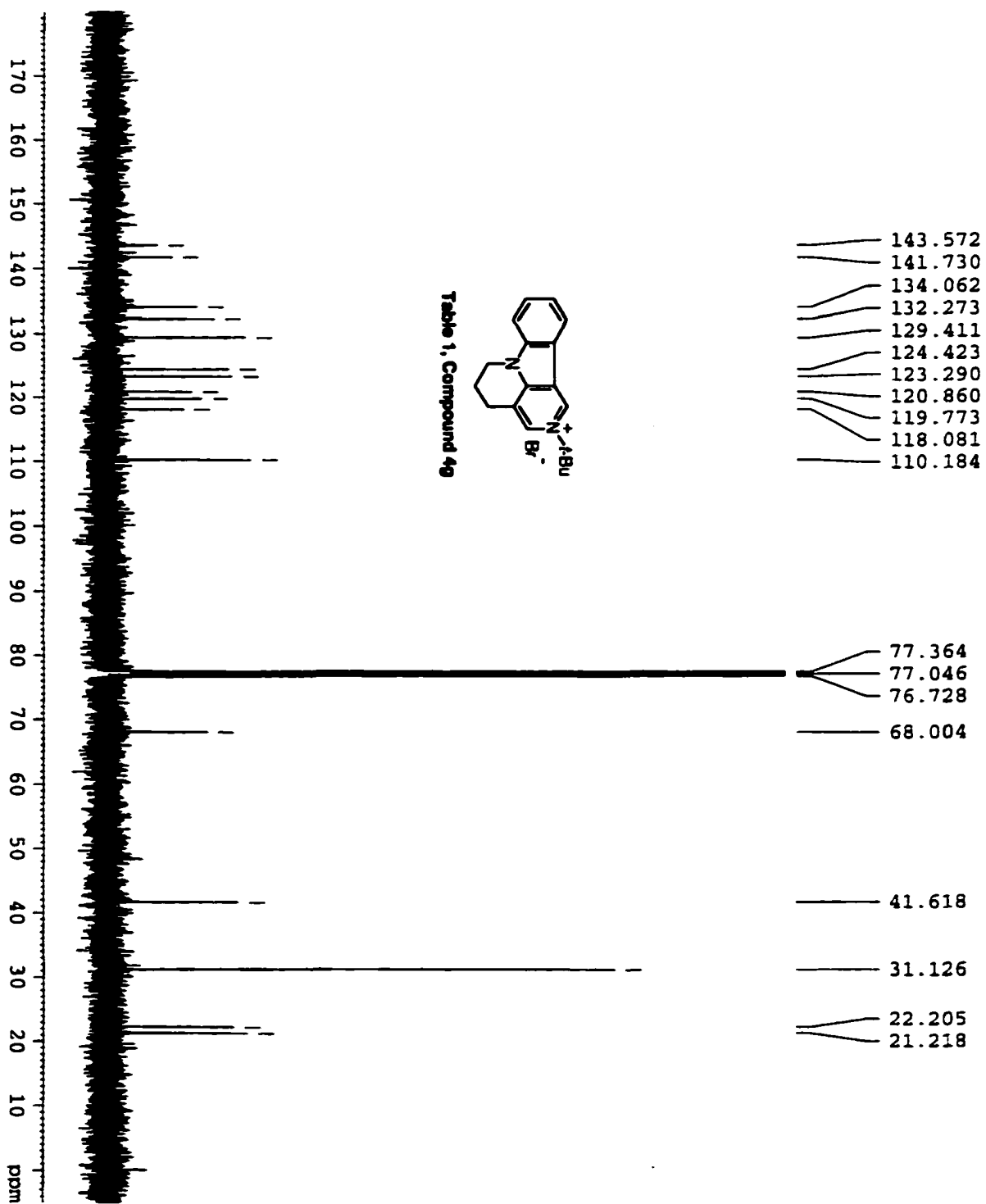


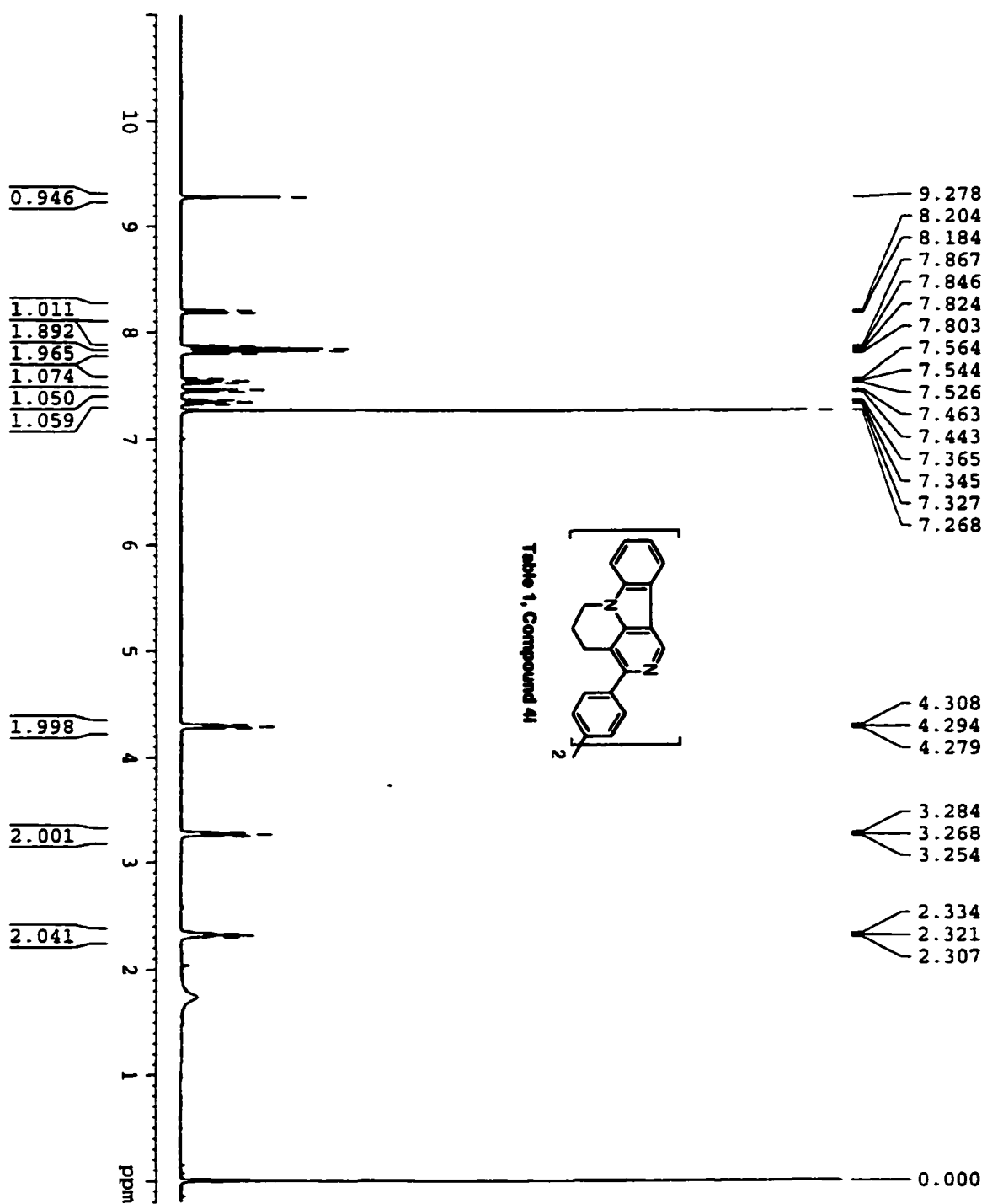












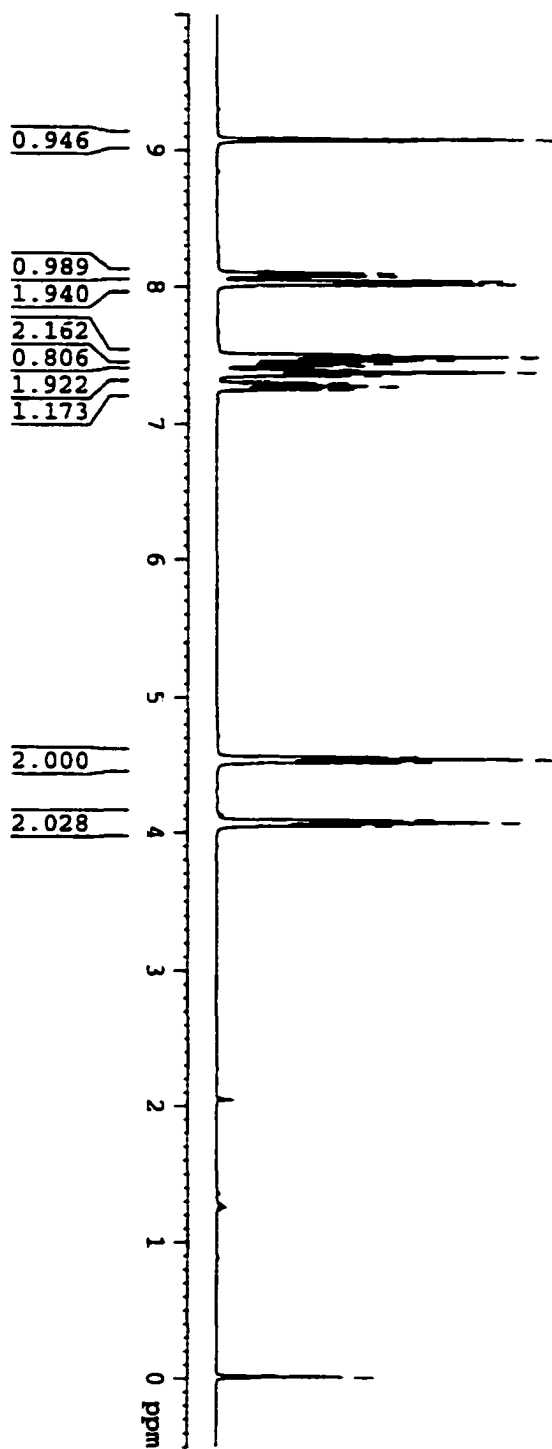
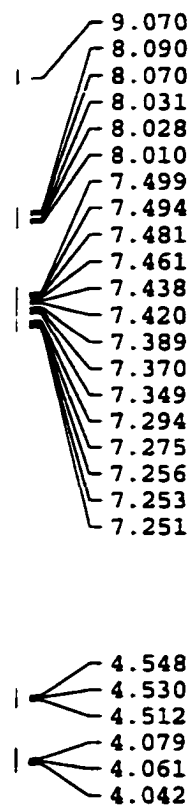
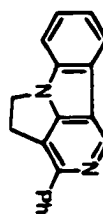
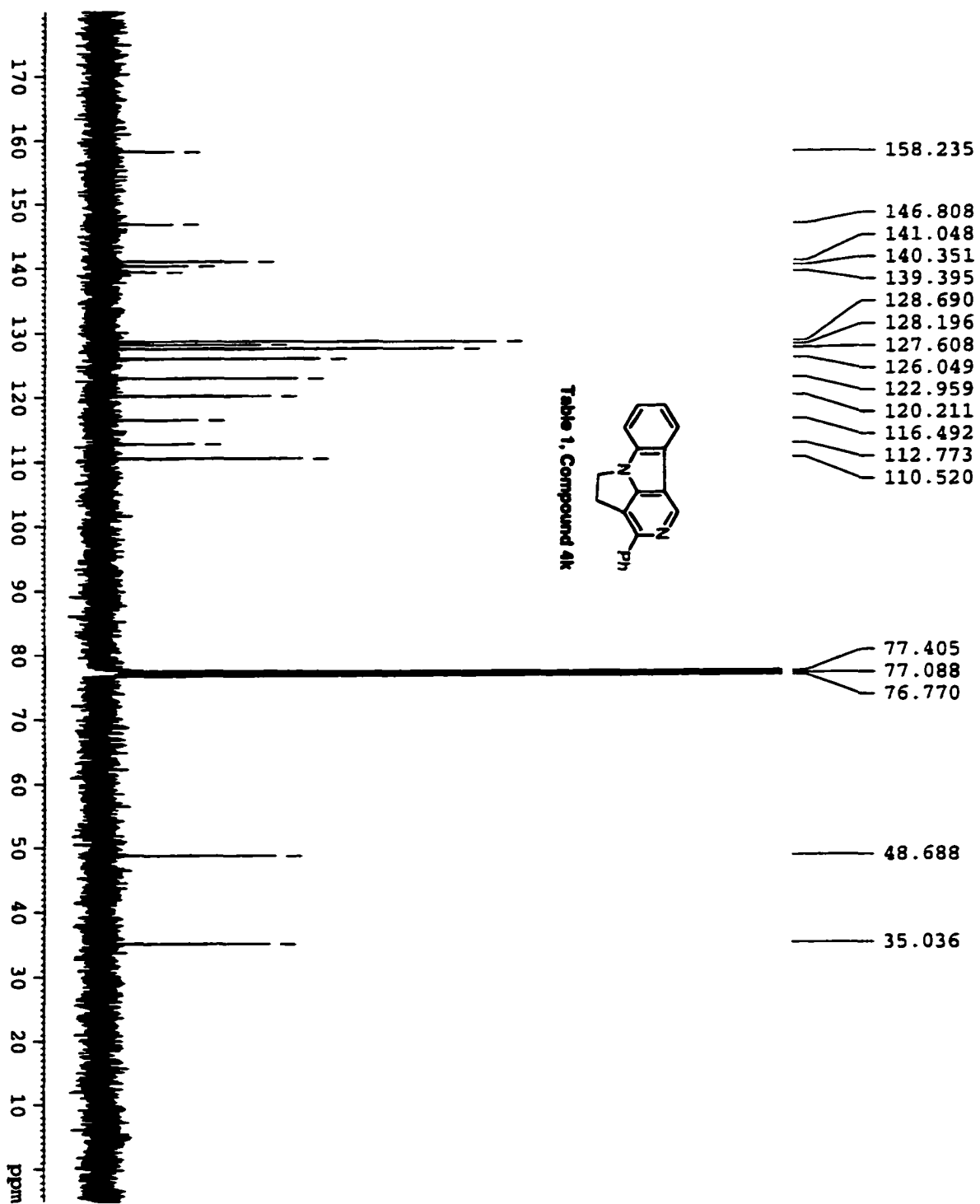
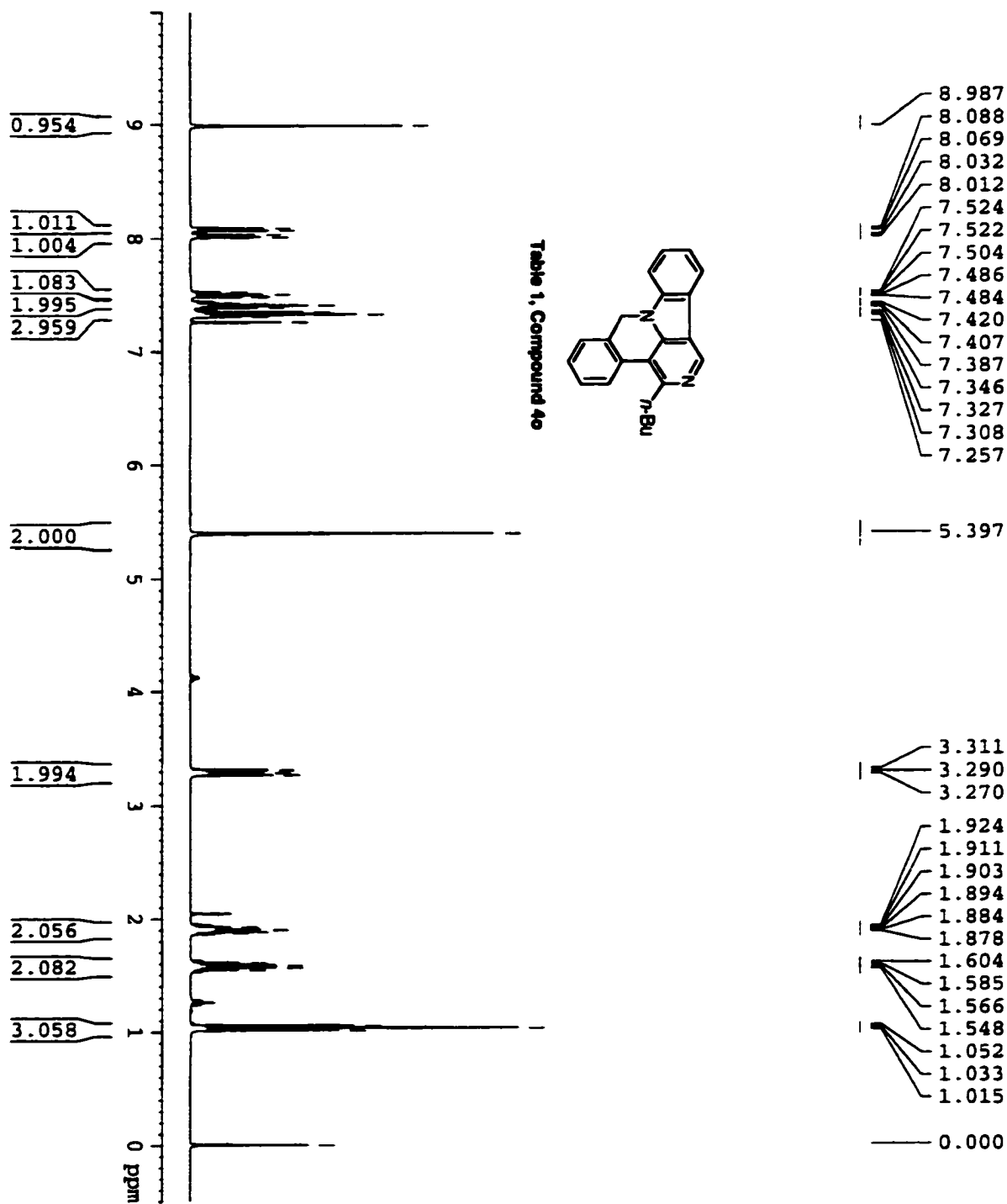


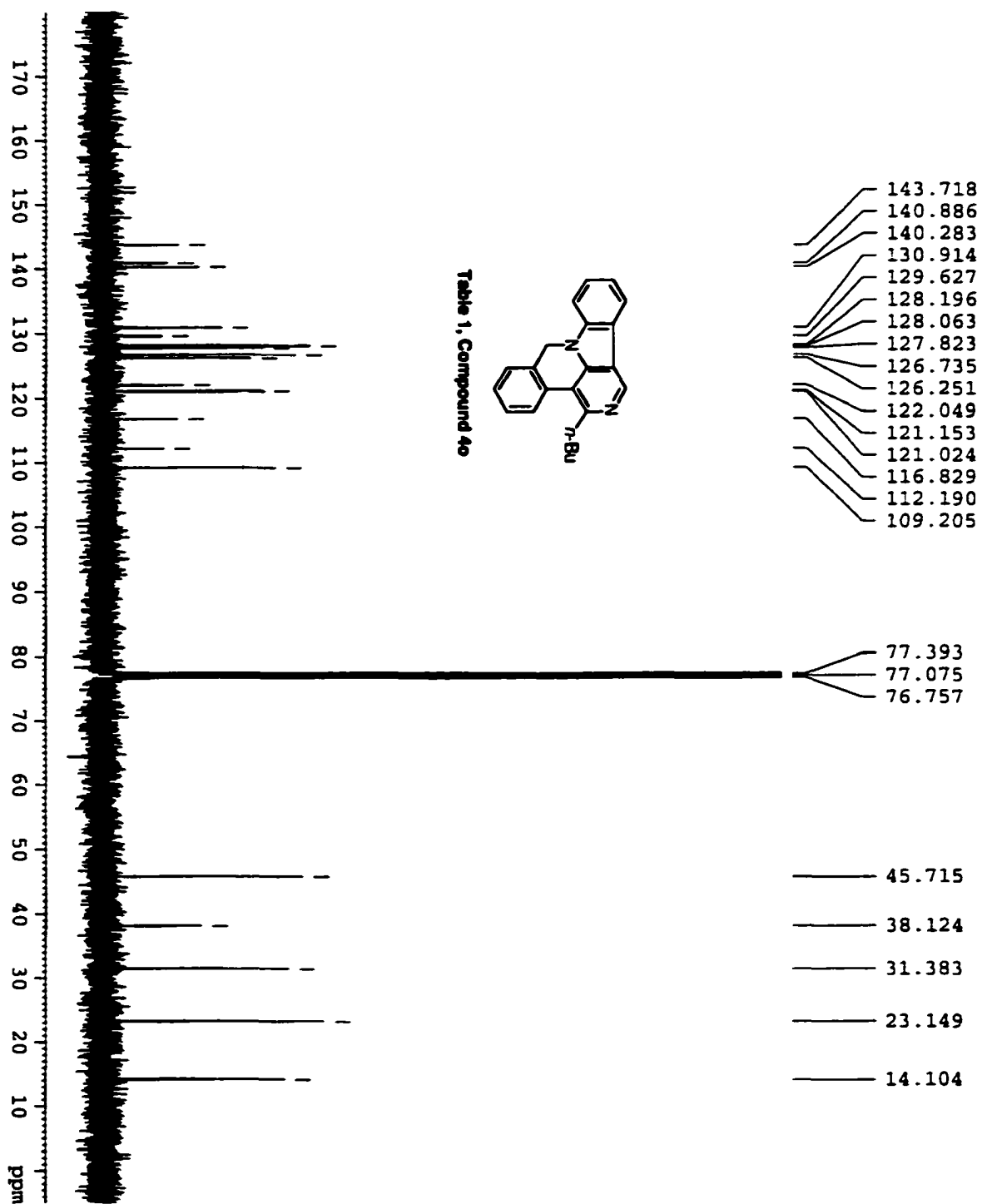
Table 1, Compound 4k

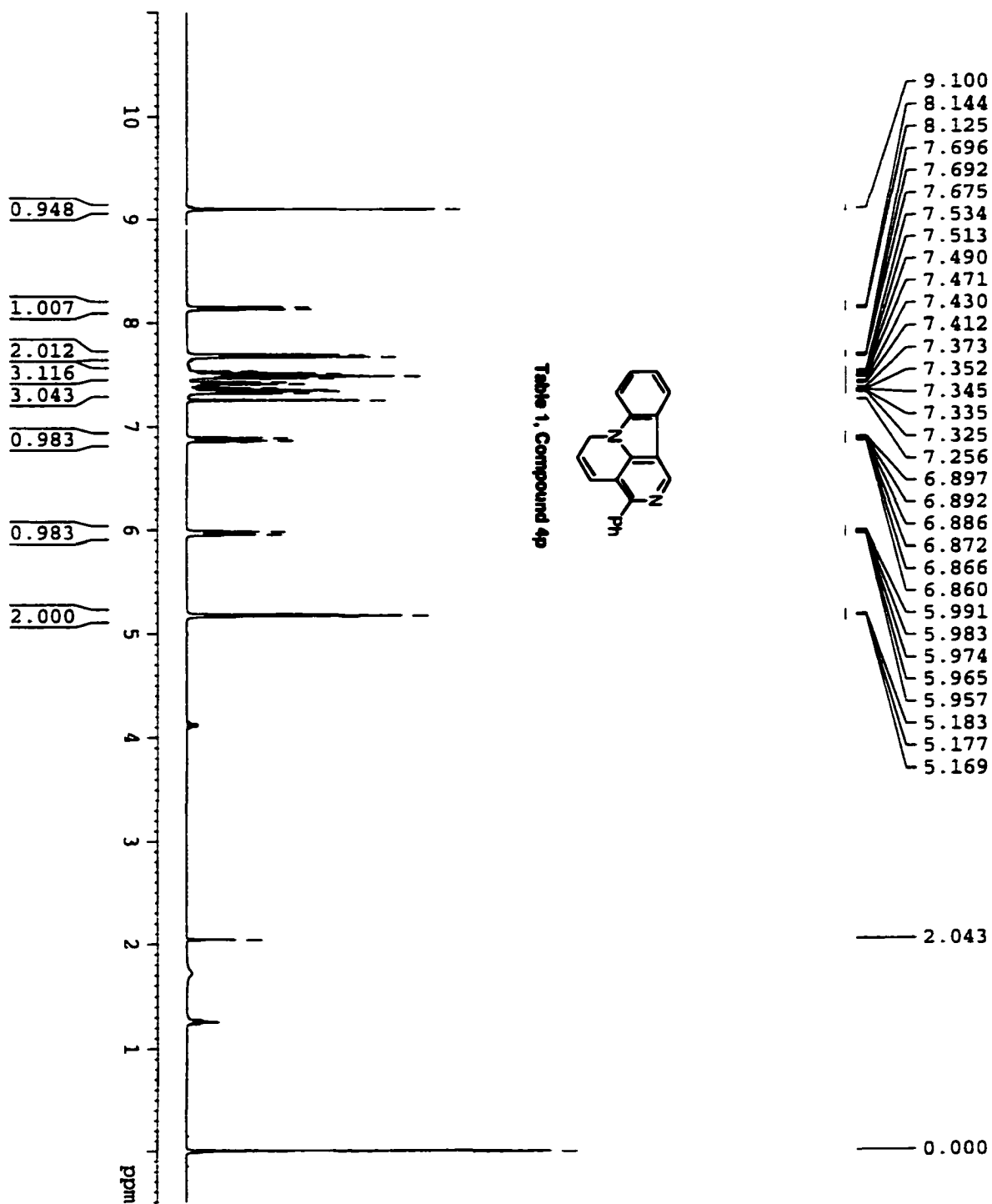


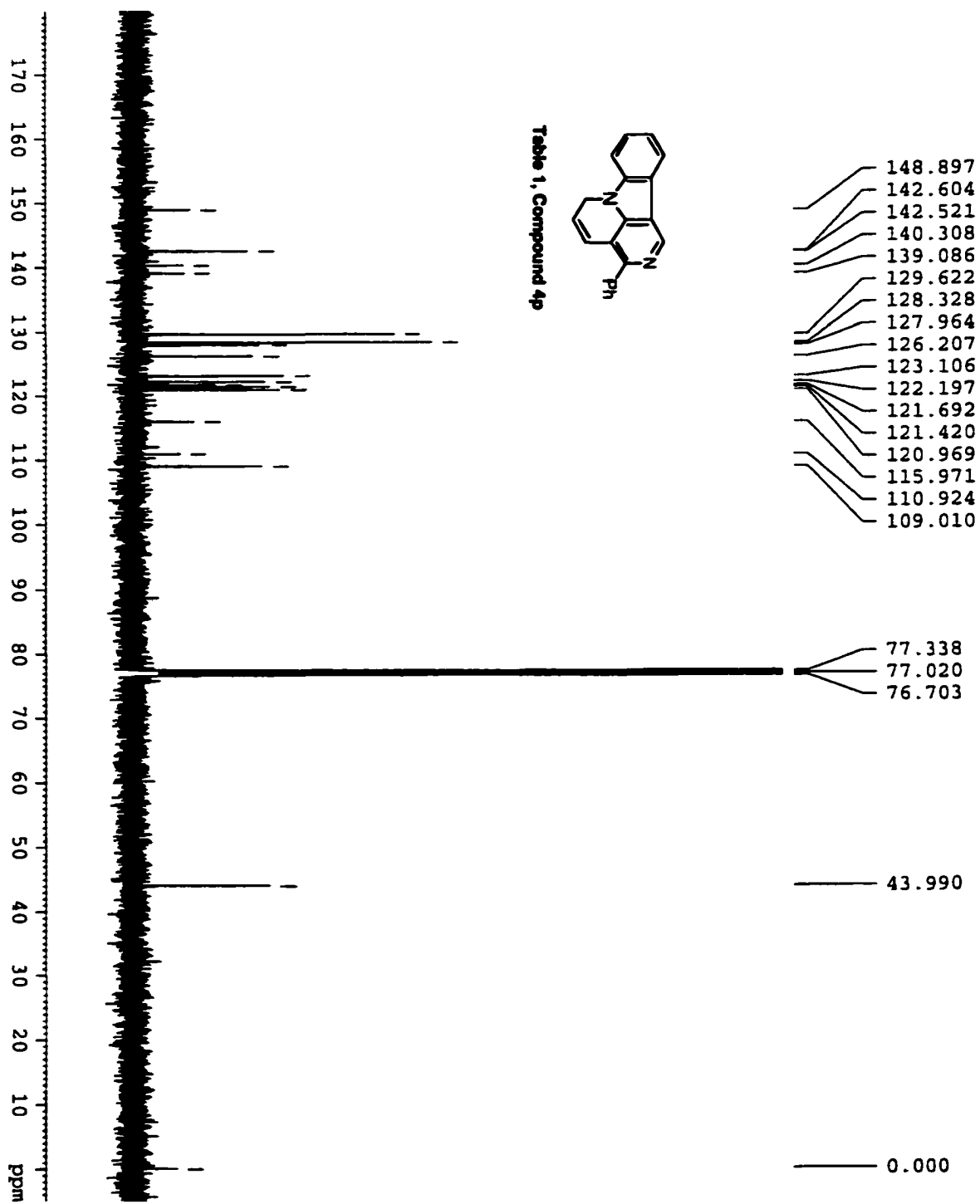
— 0.000



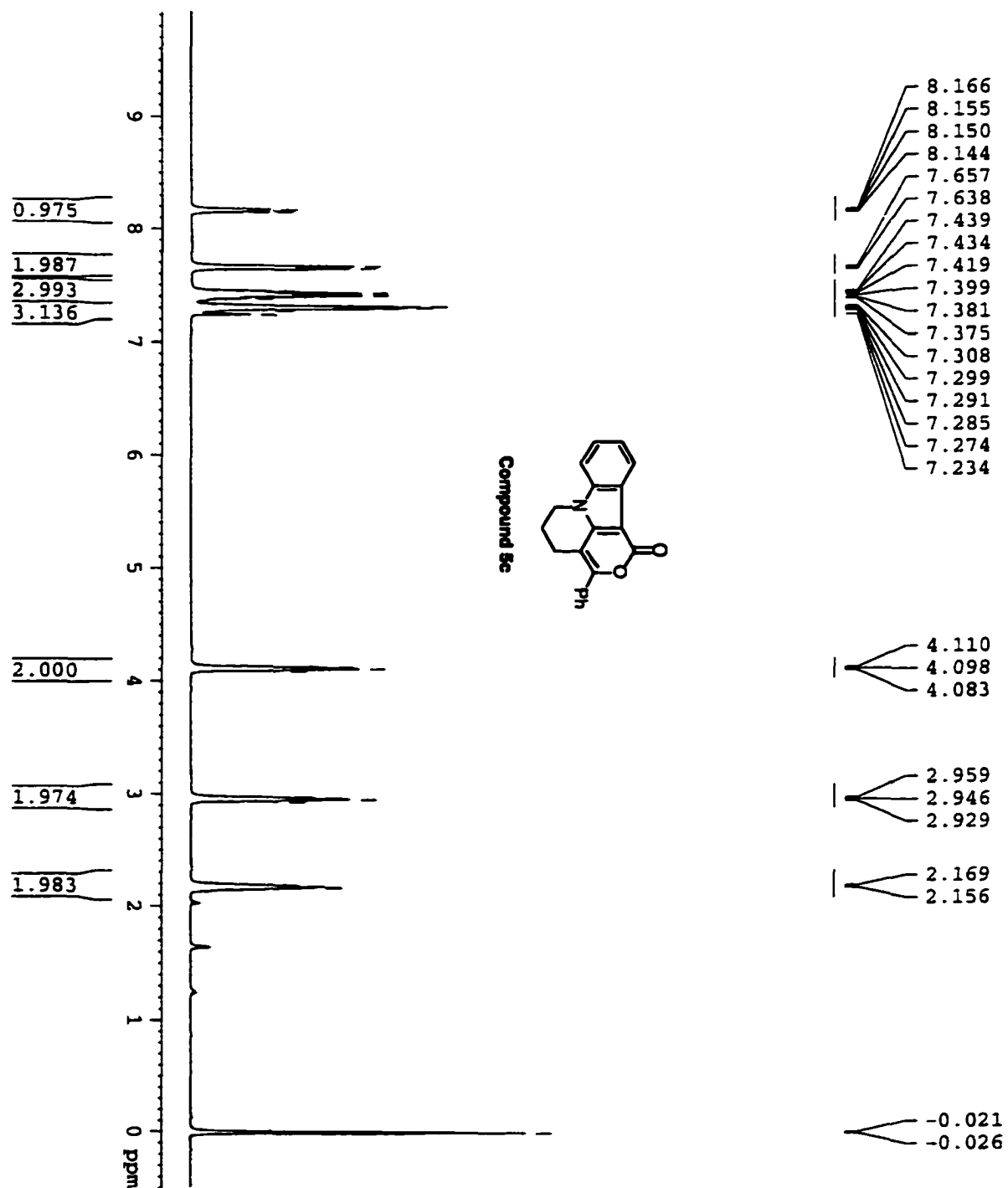


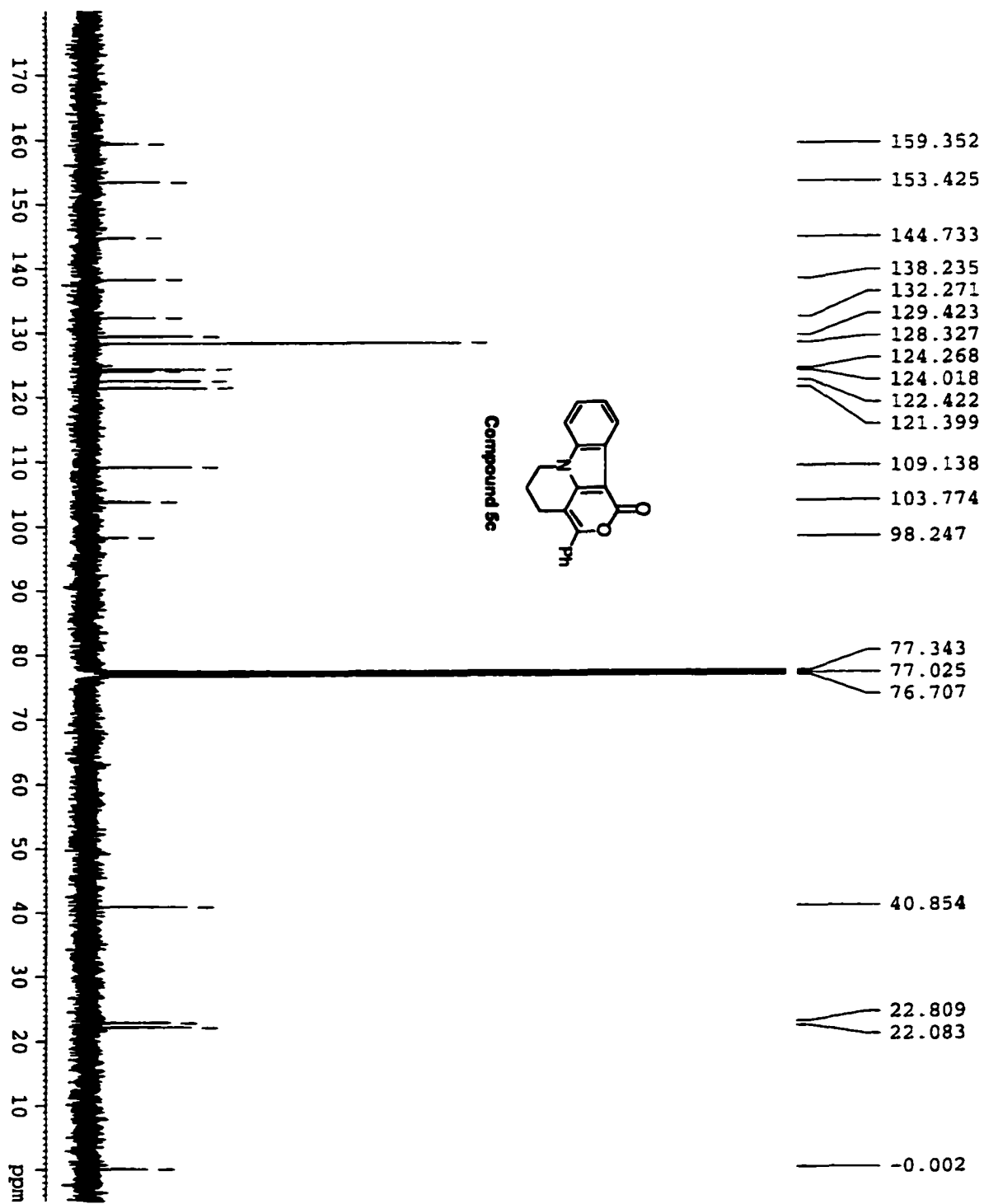


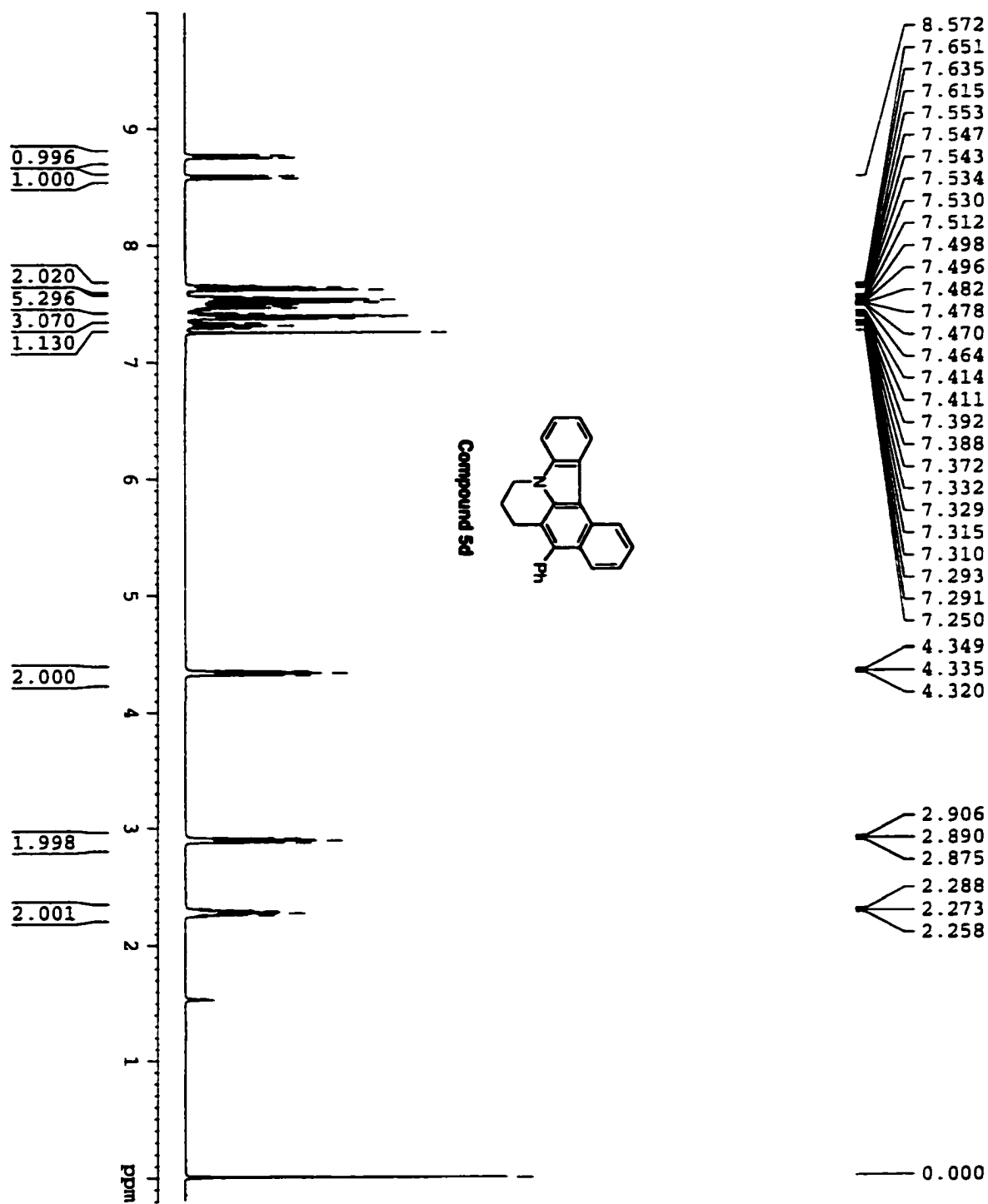


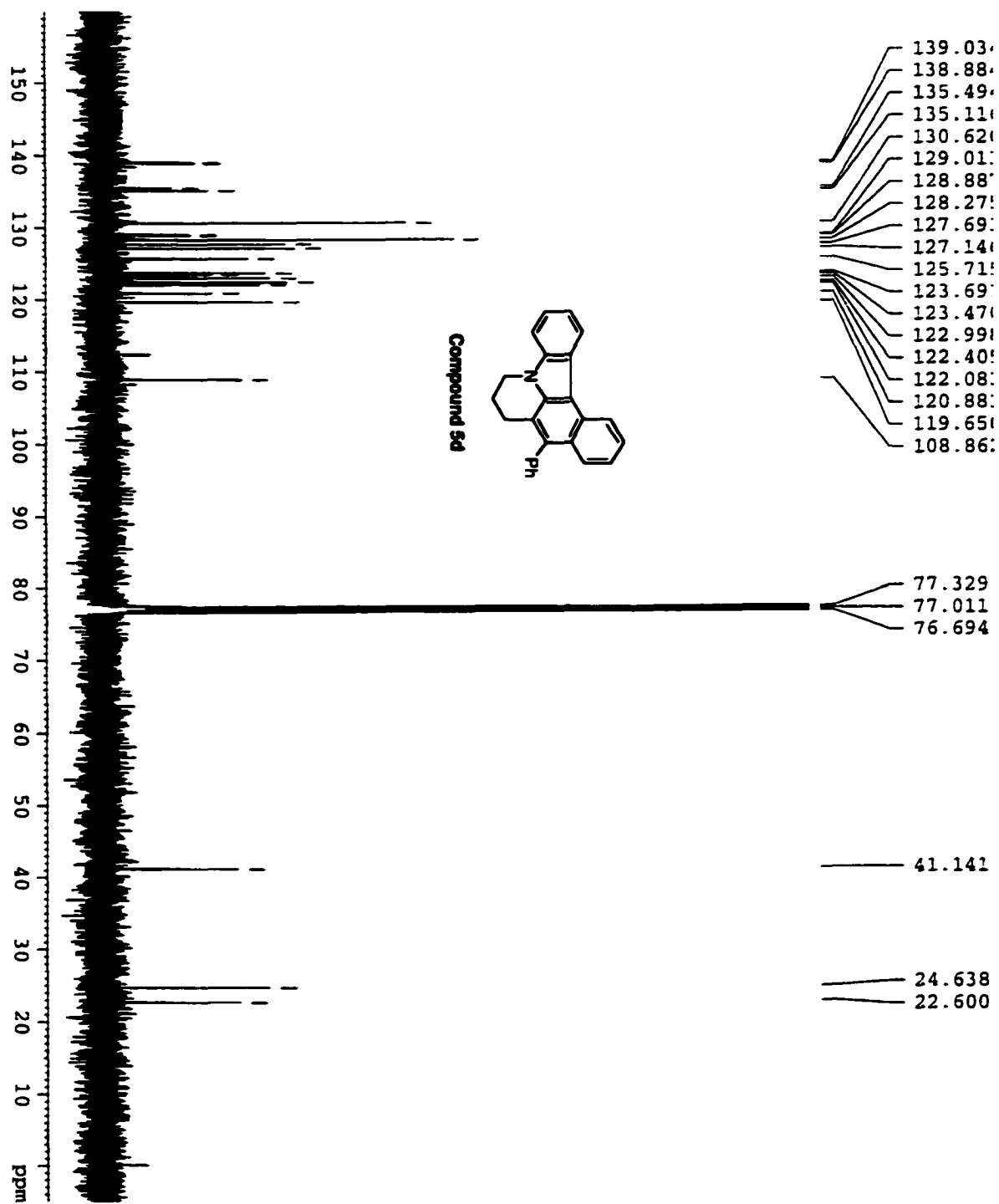
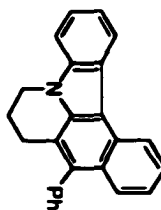




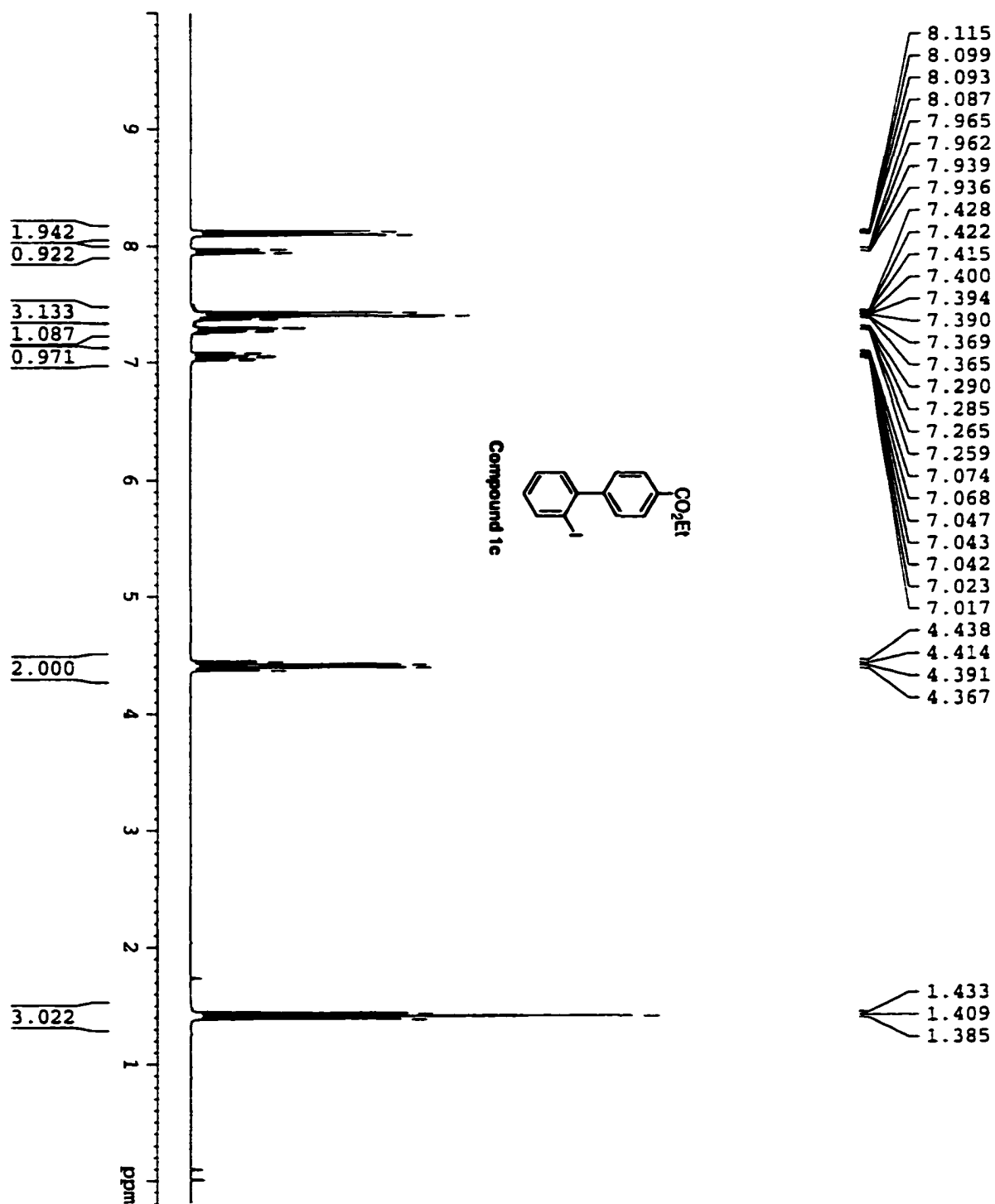


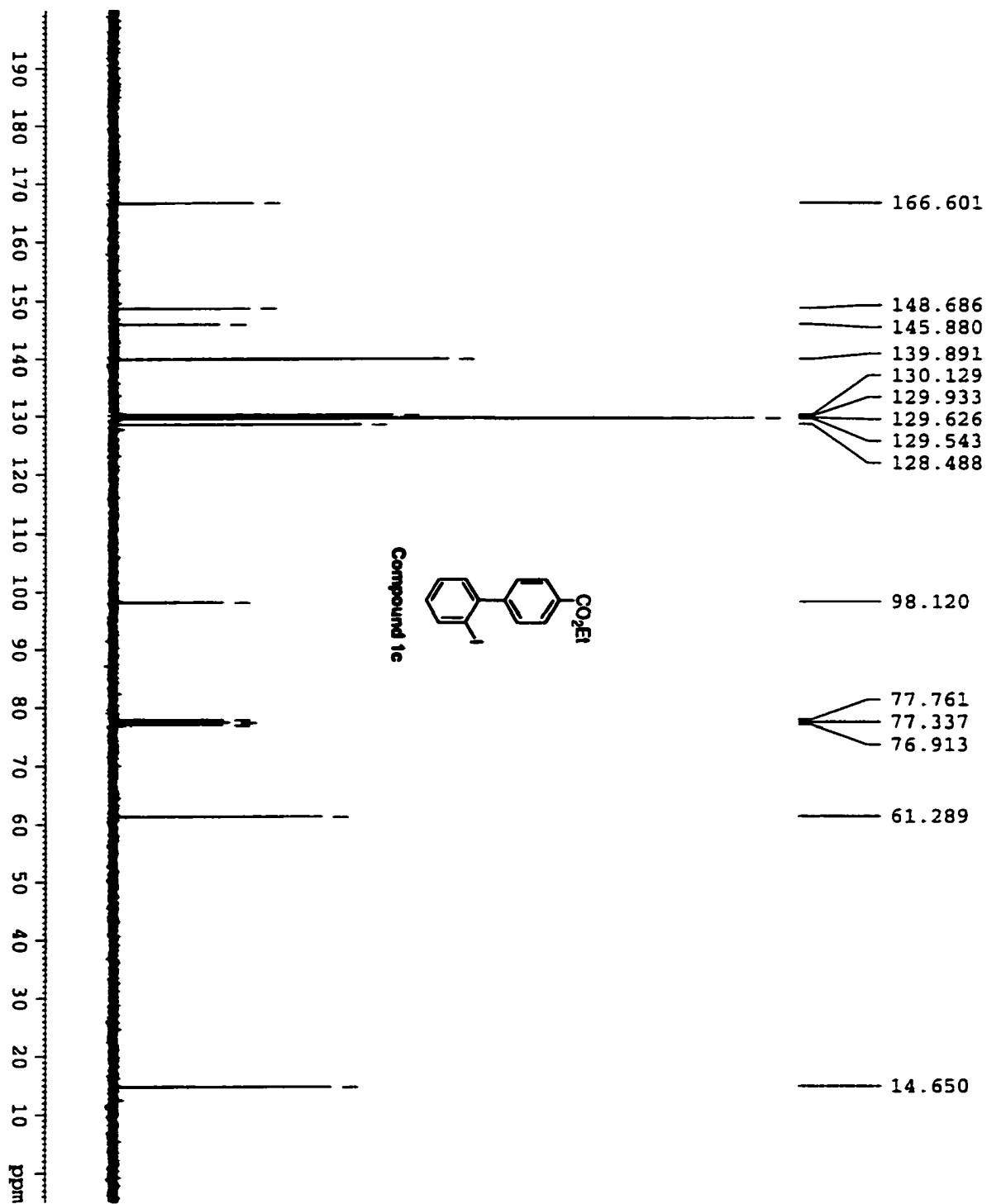


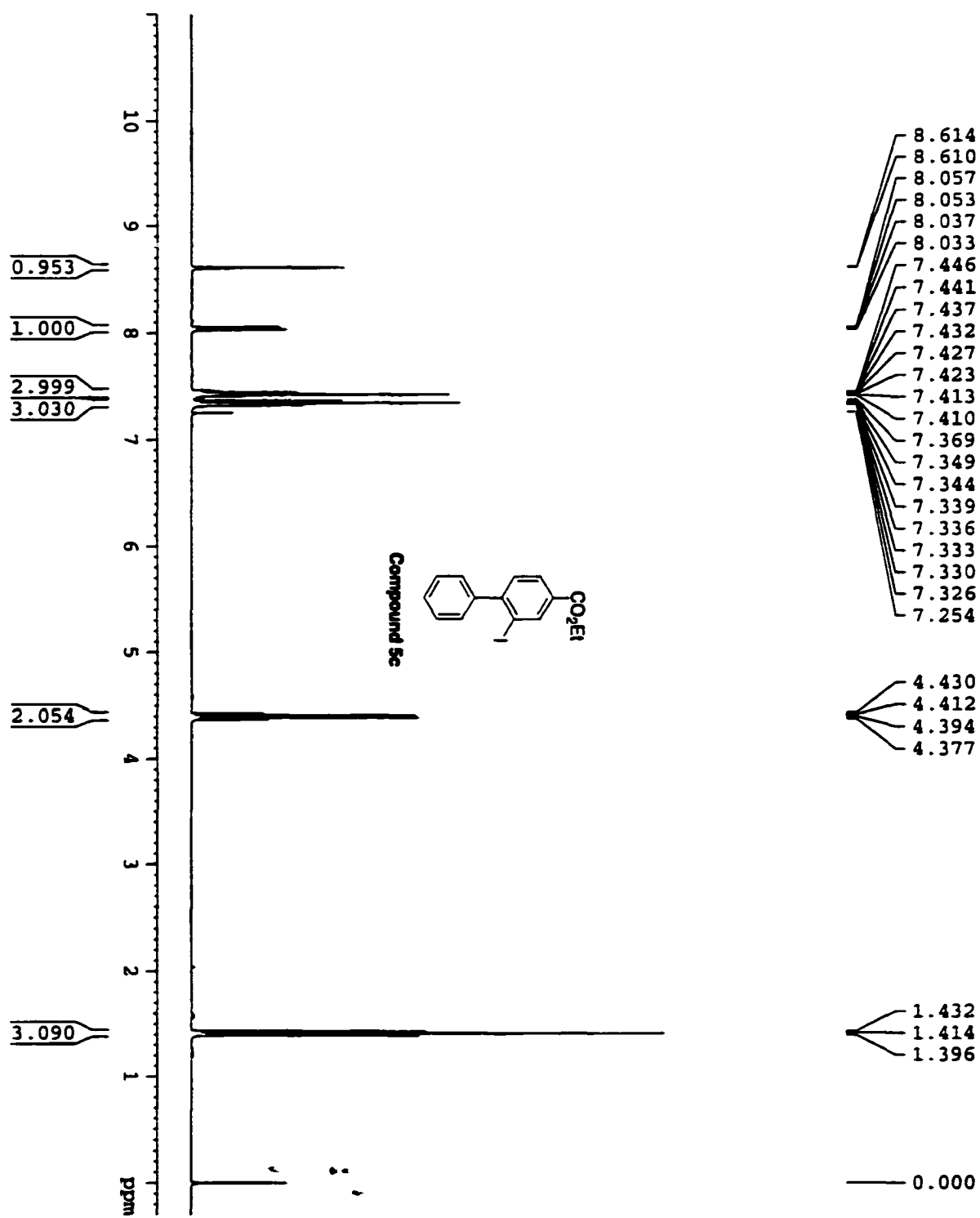




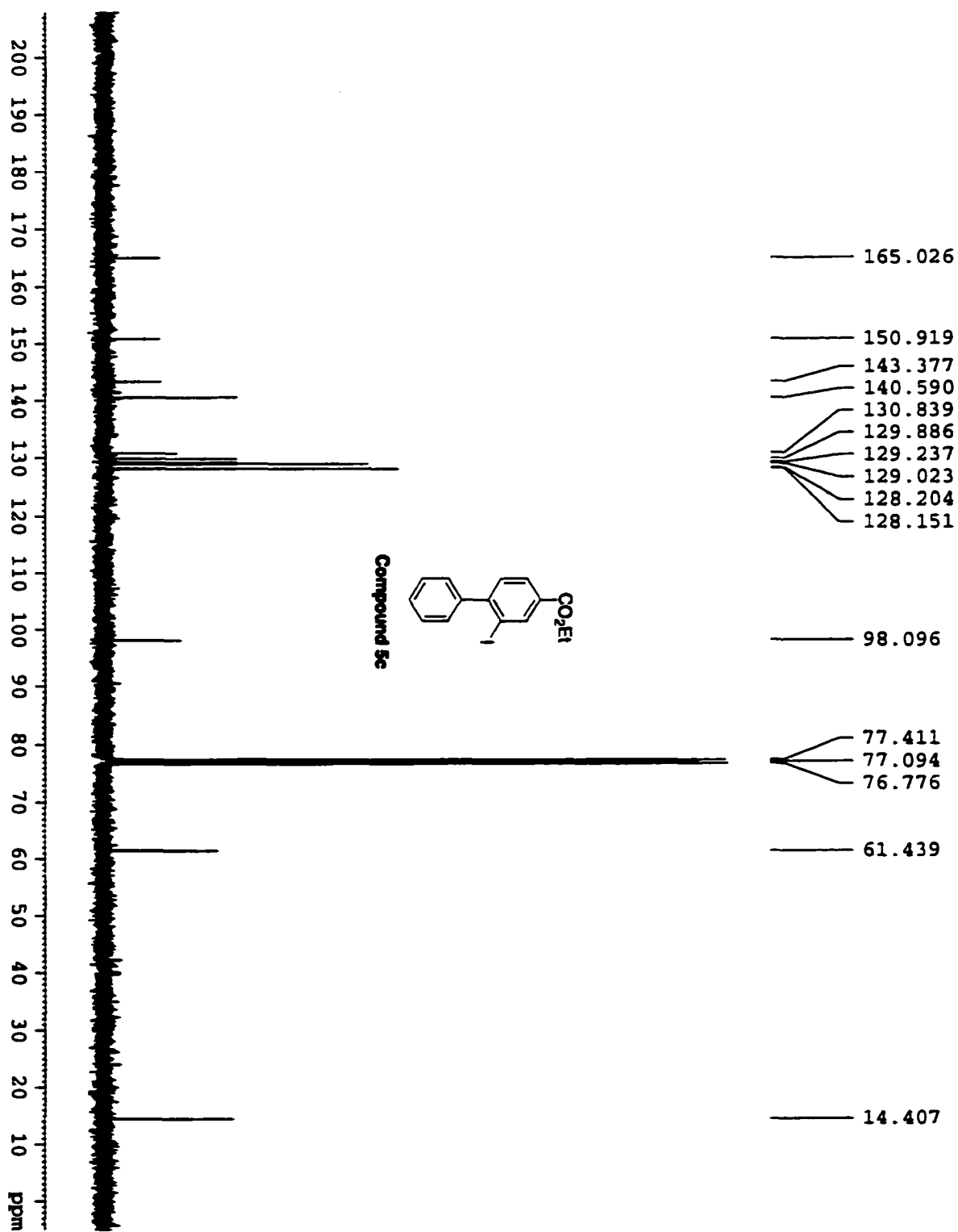
**APPENDIX D. CHAPTER 4  $^1\text{H}$  AND  $^{13}\text{C}$  NMR SPECTRA**

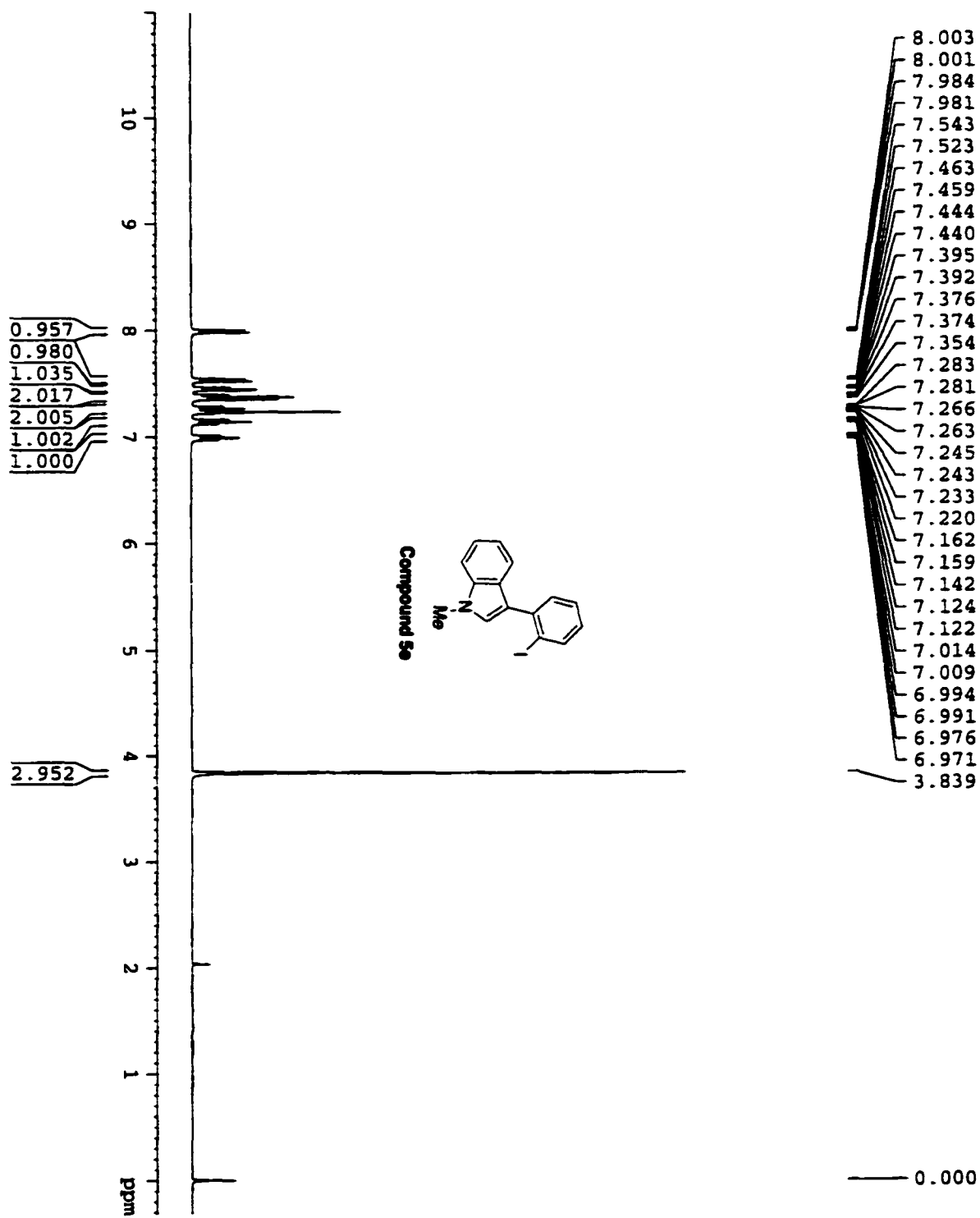


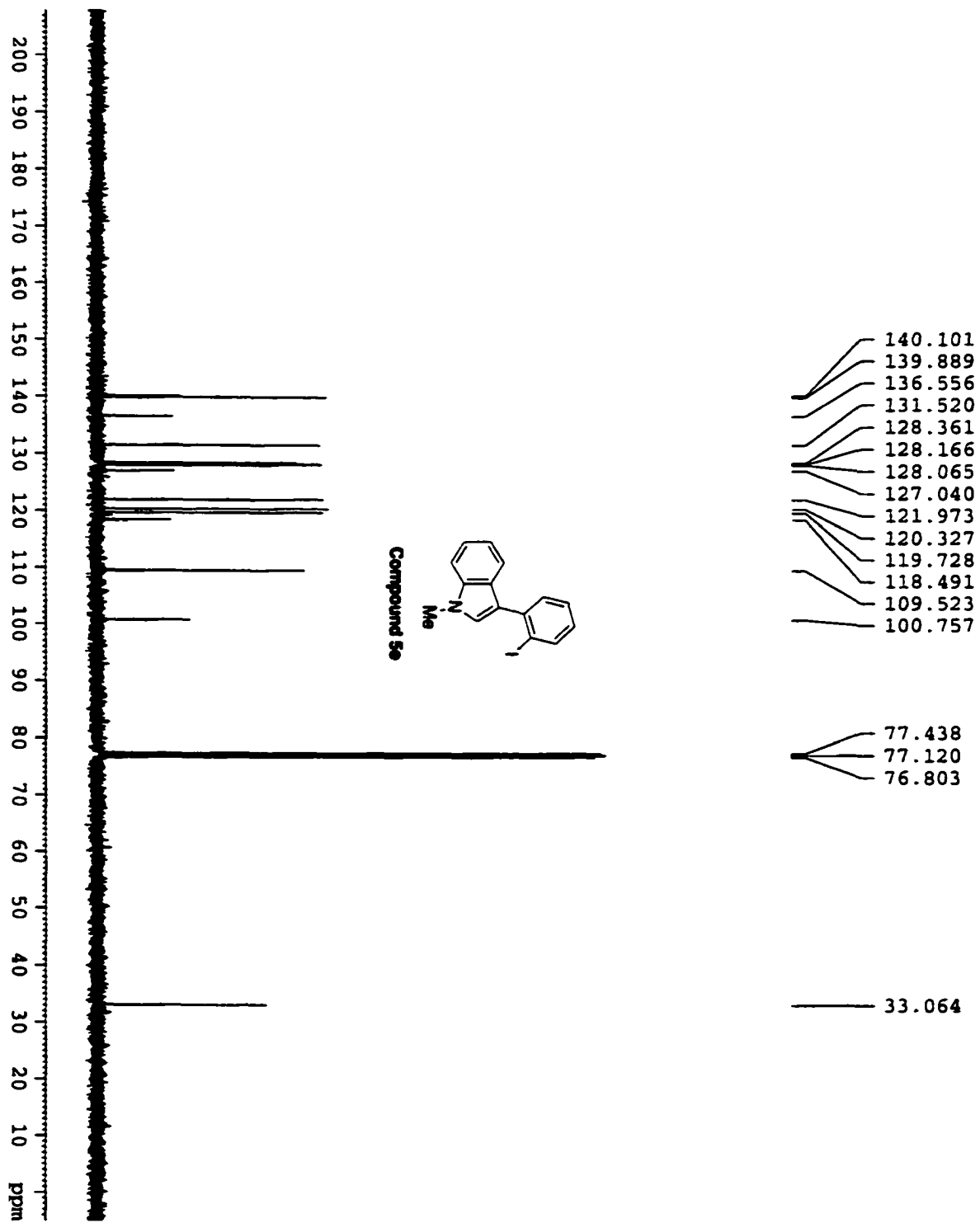


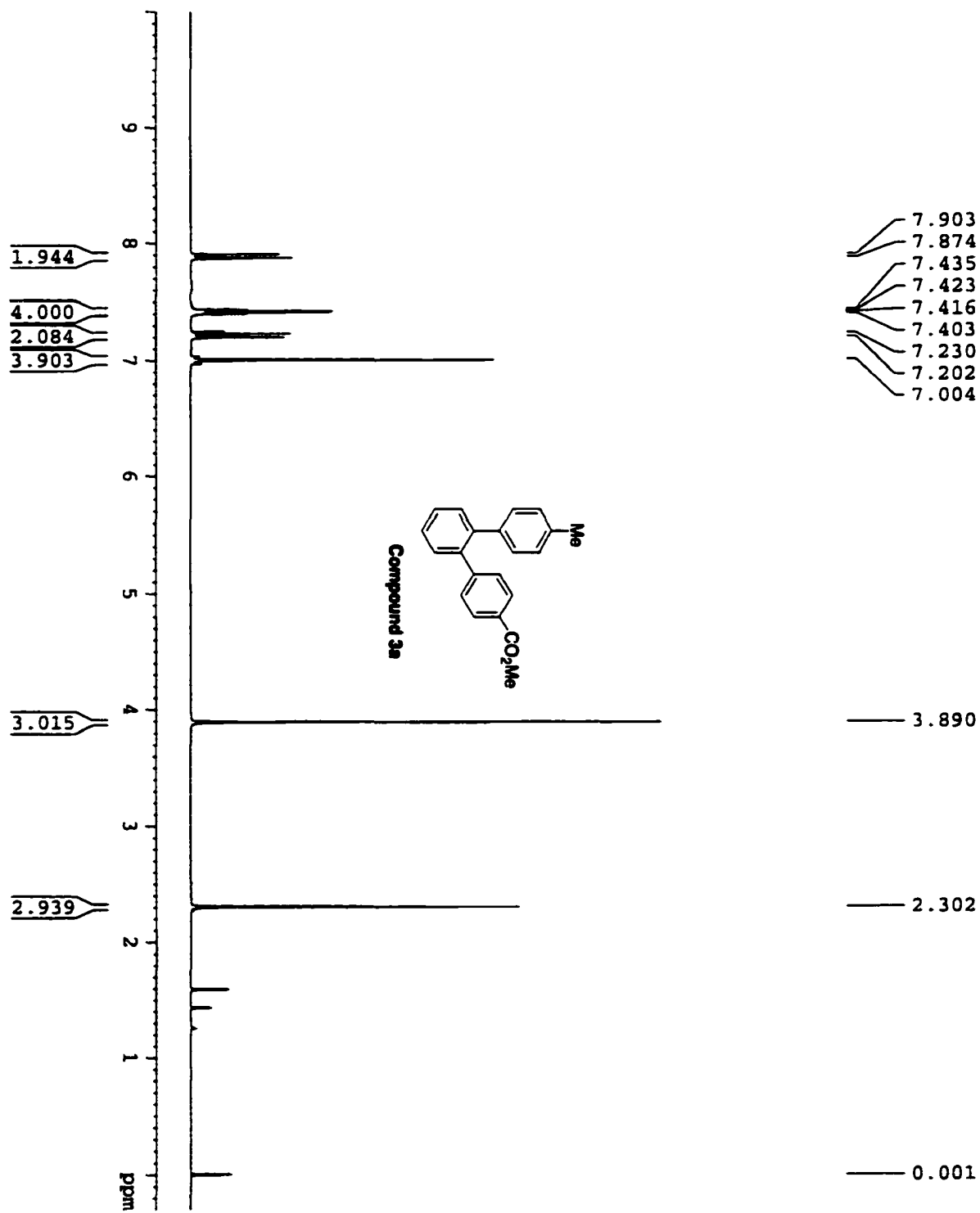


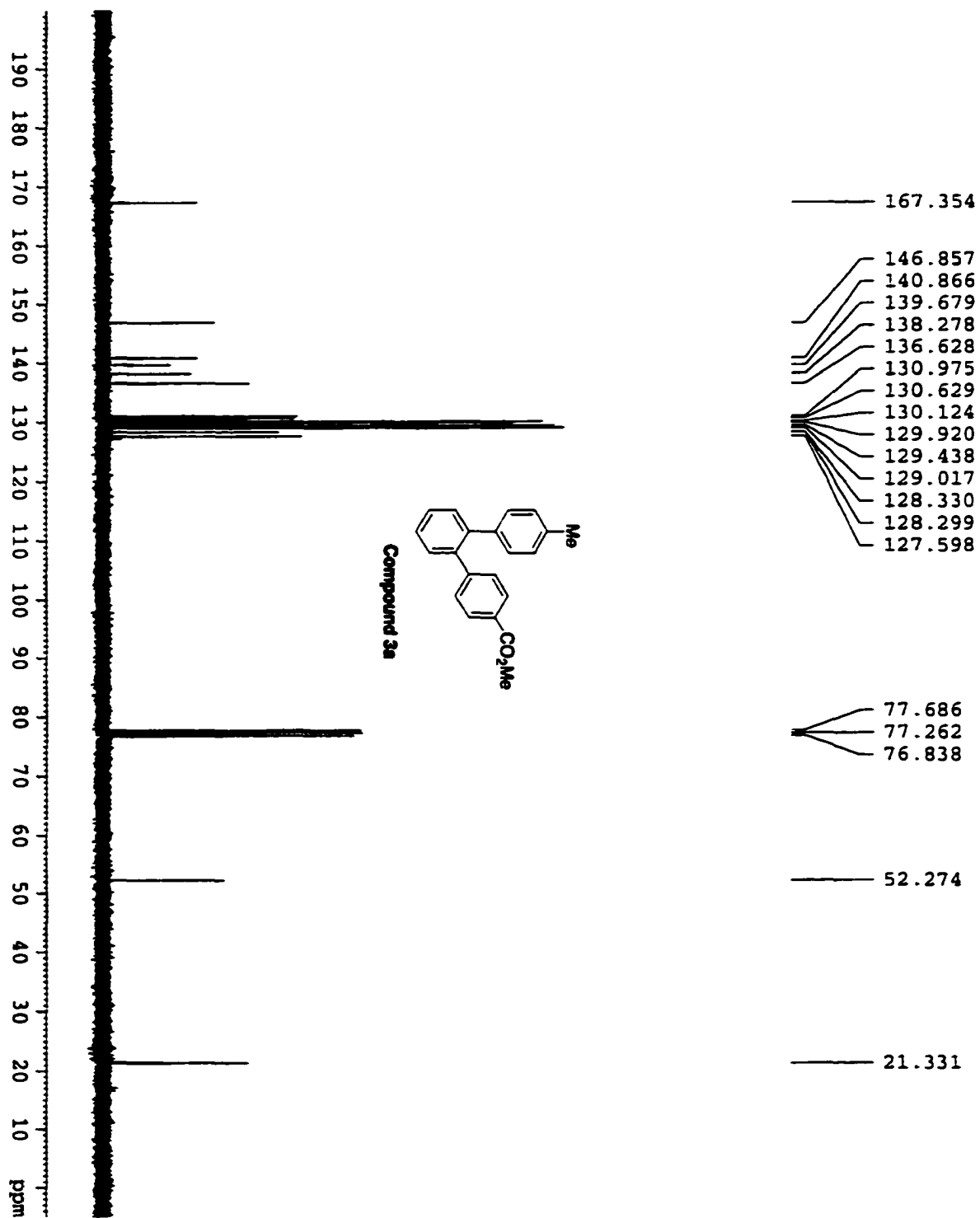


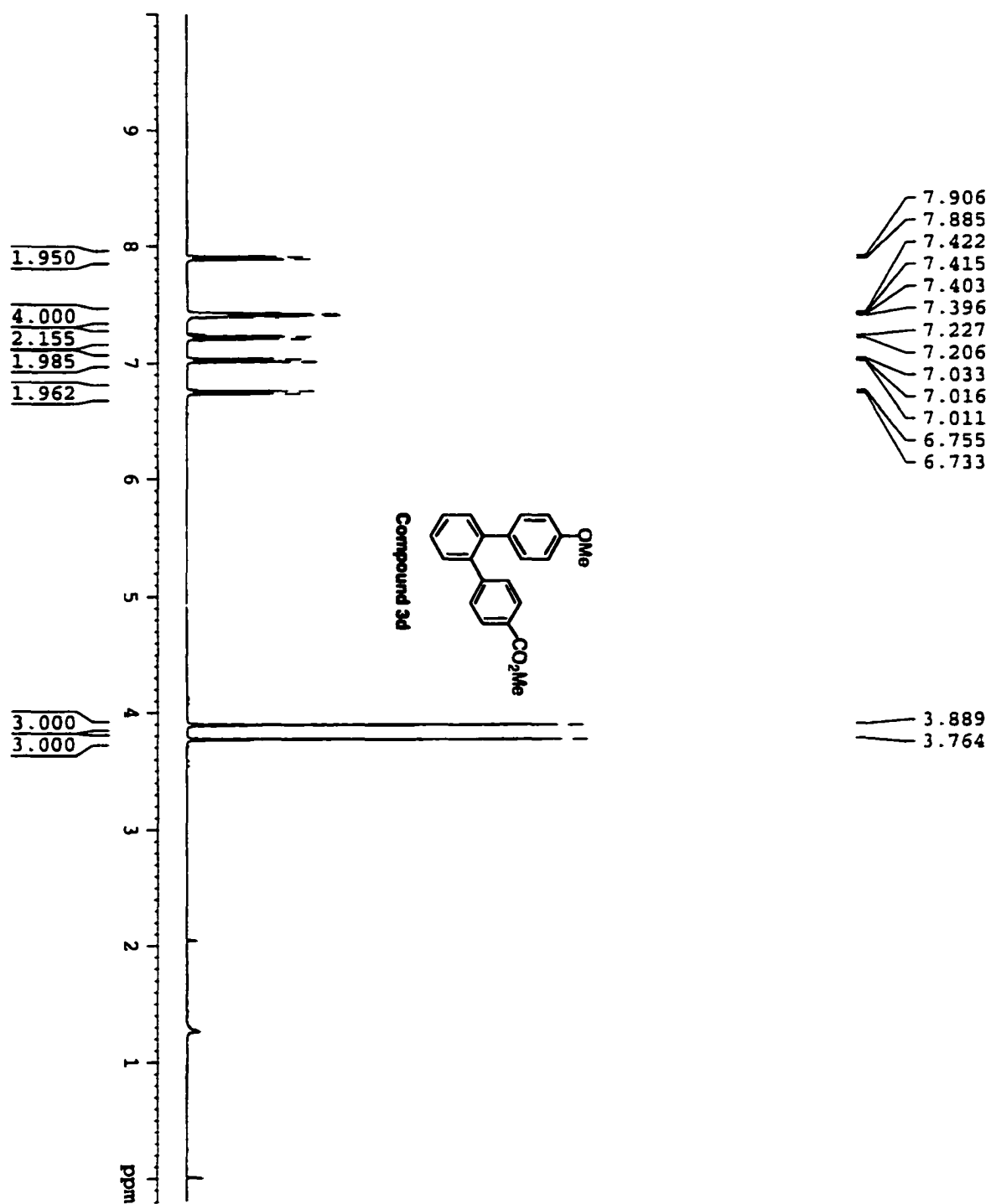


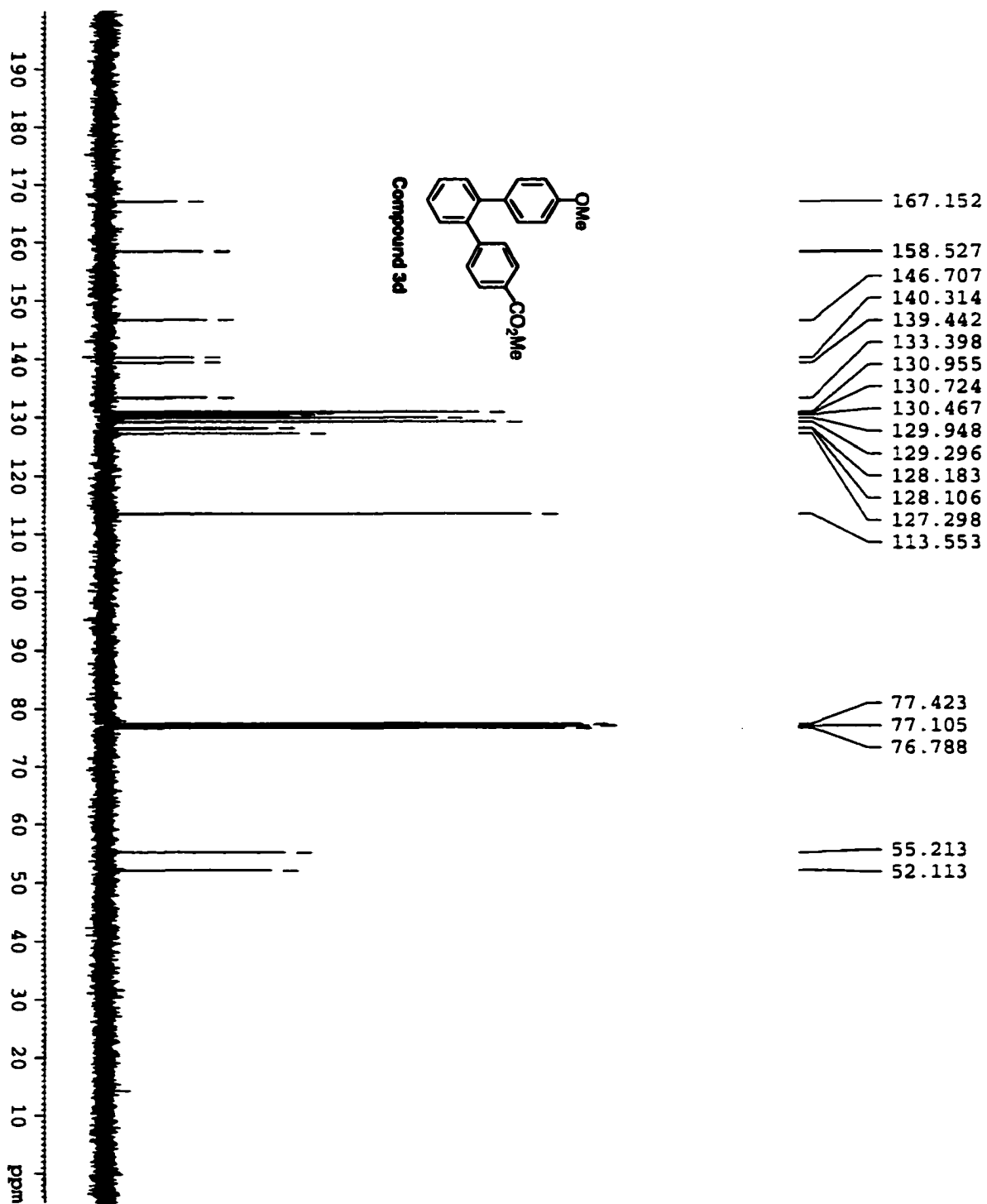


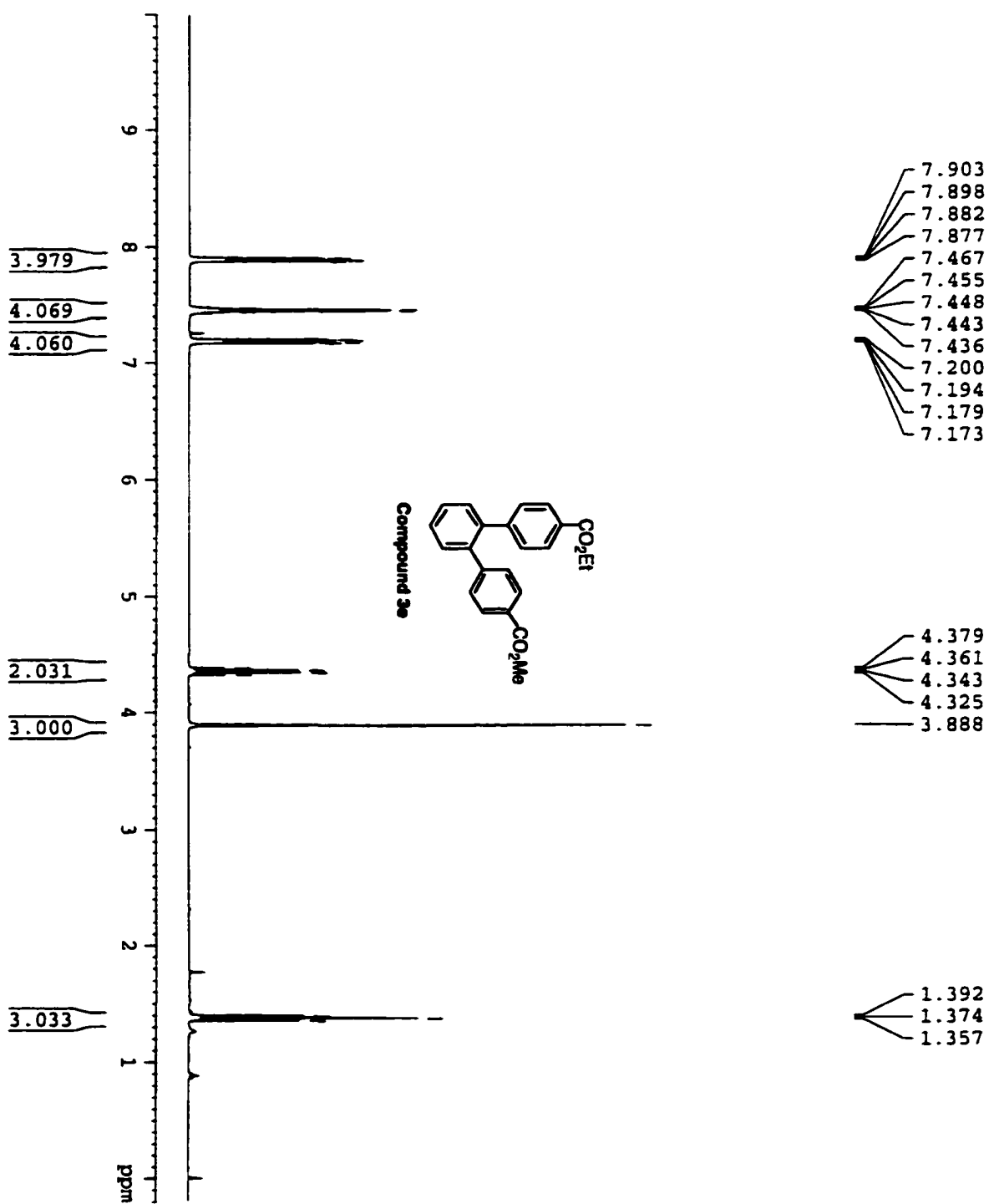




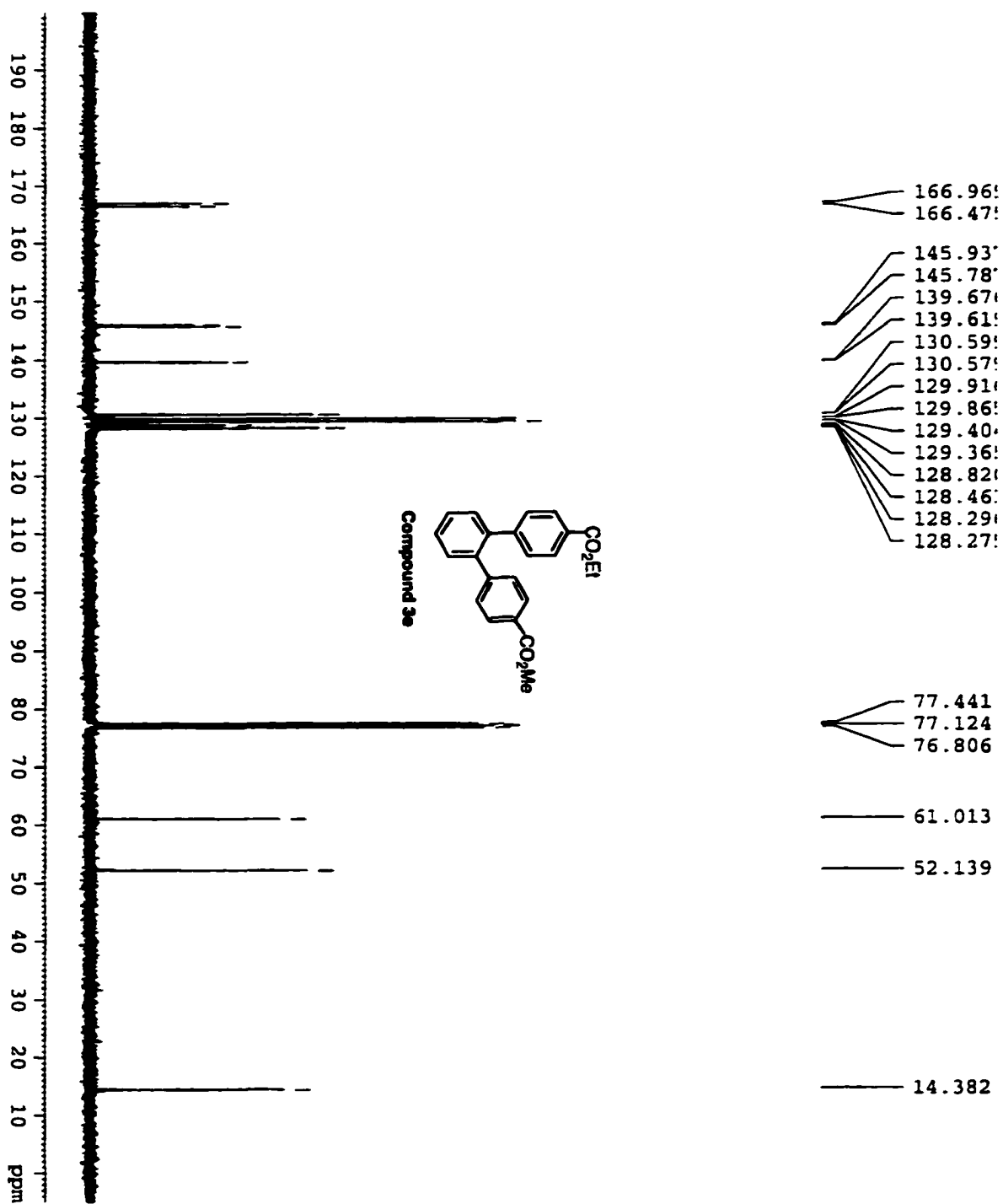


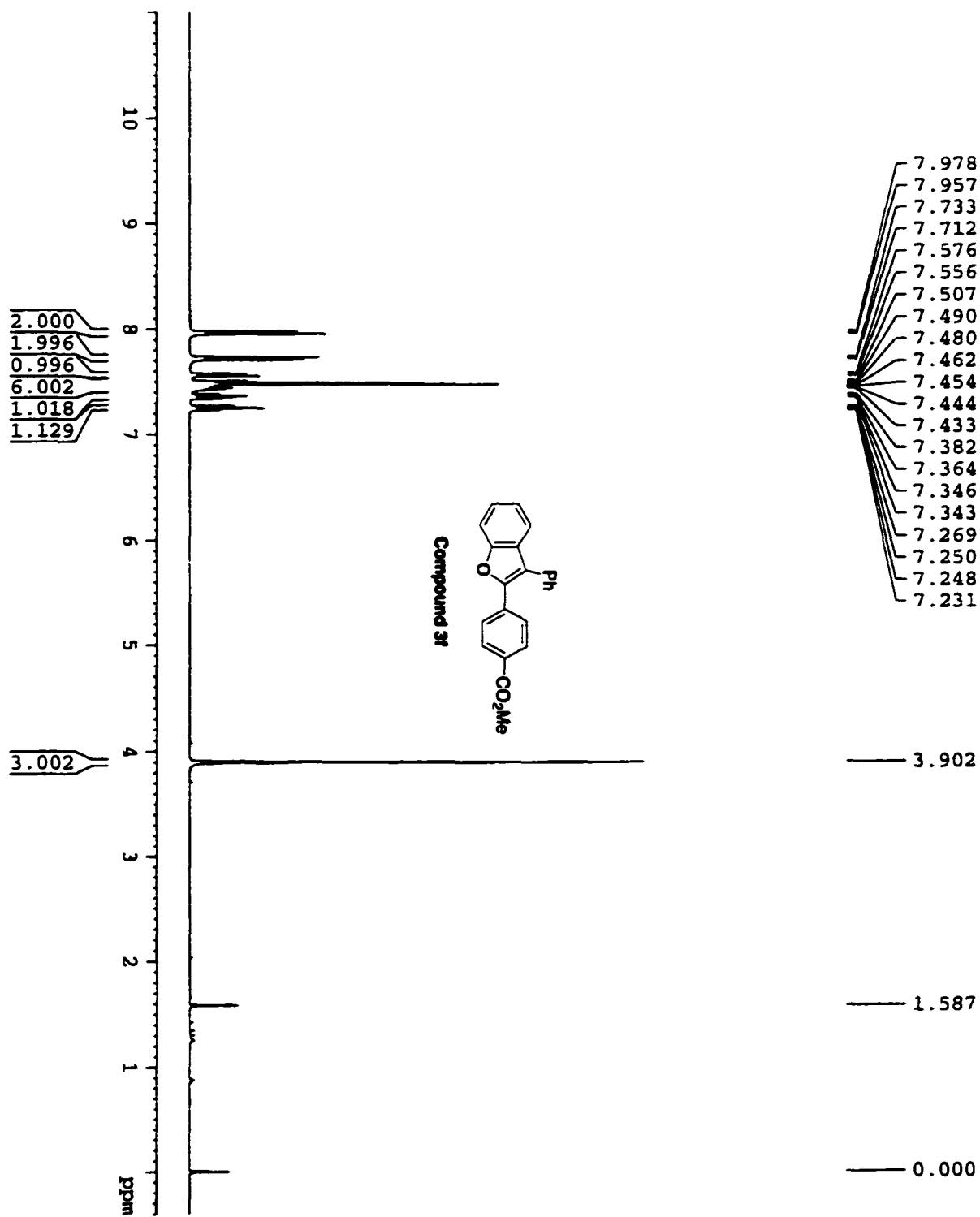


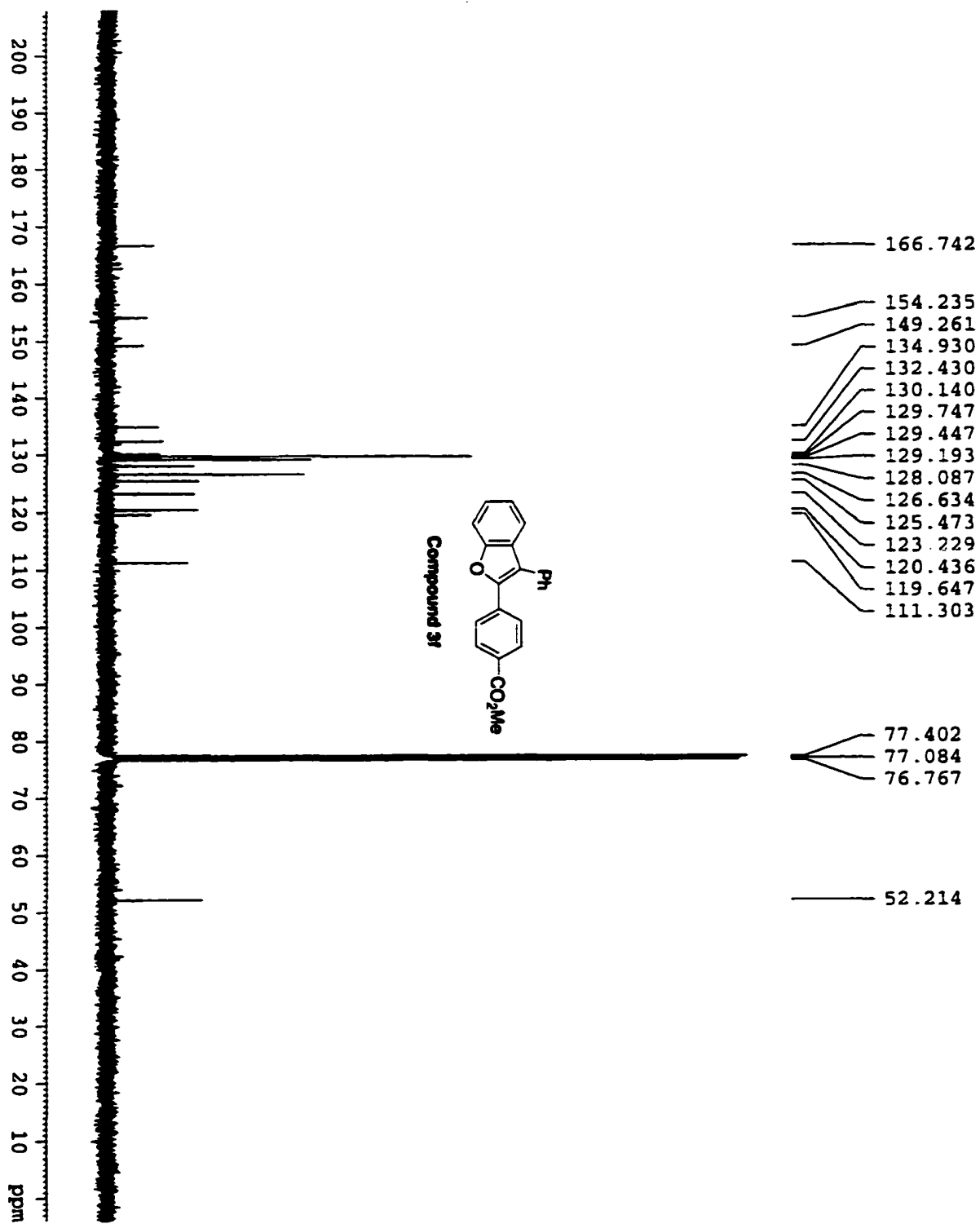


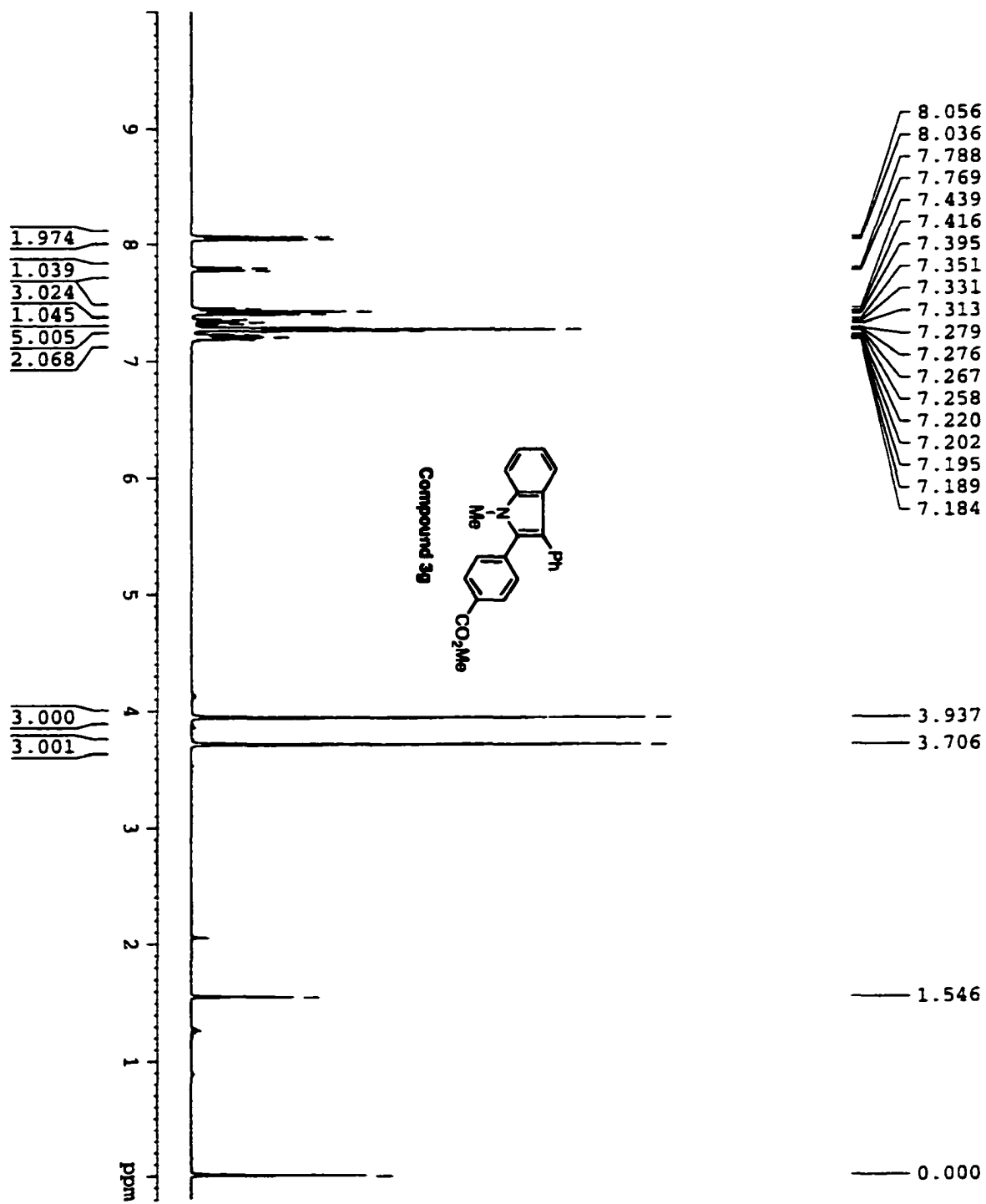


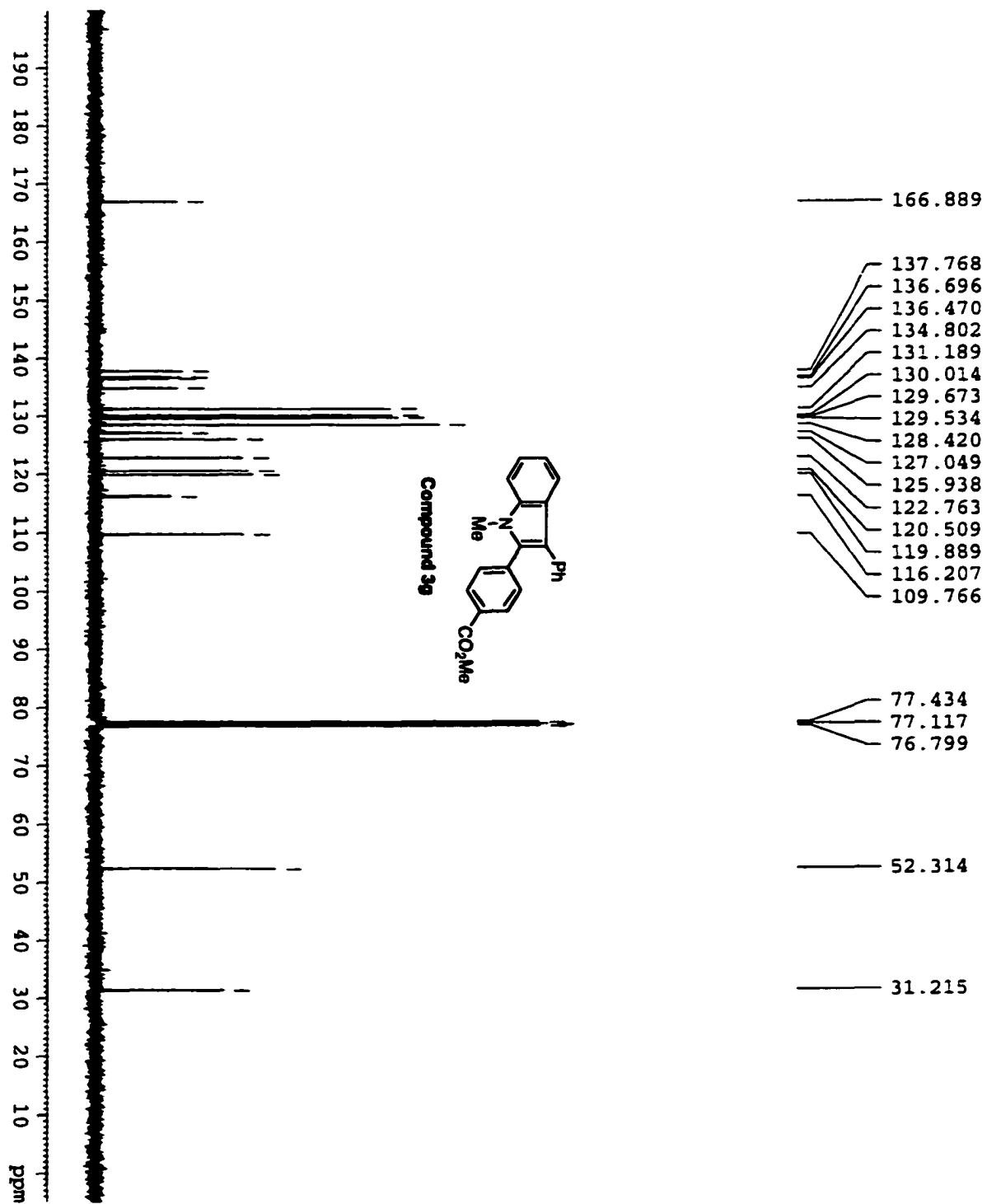


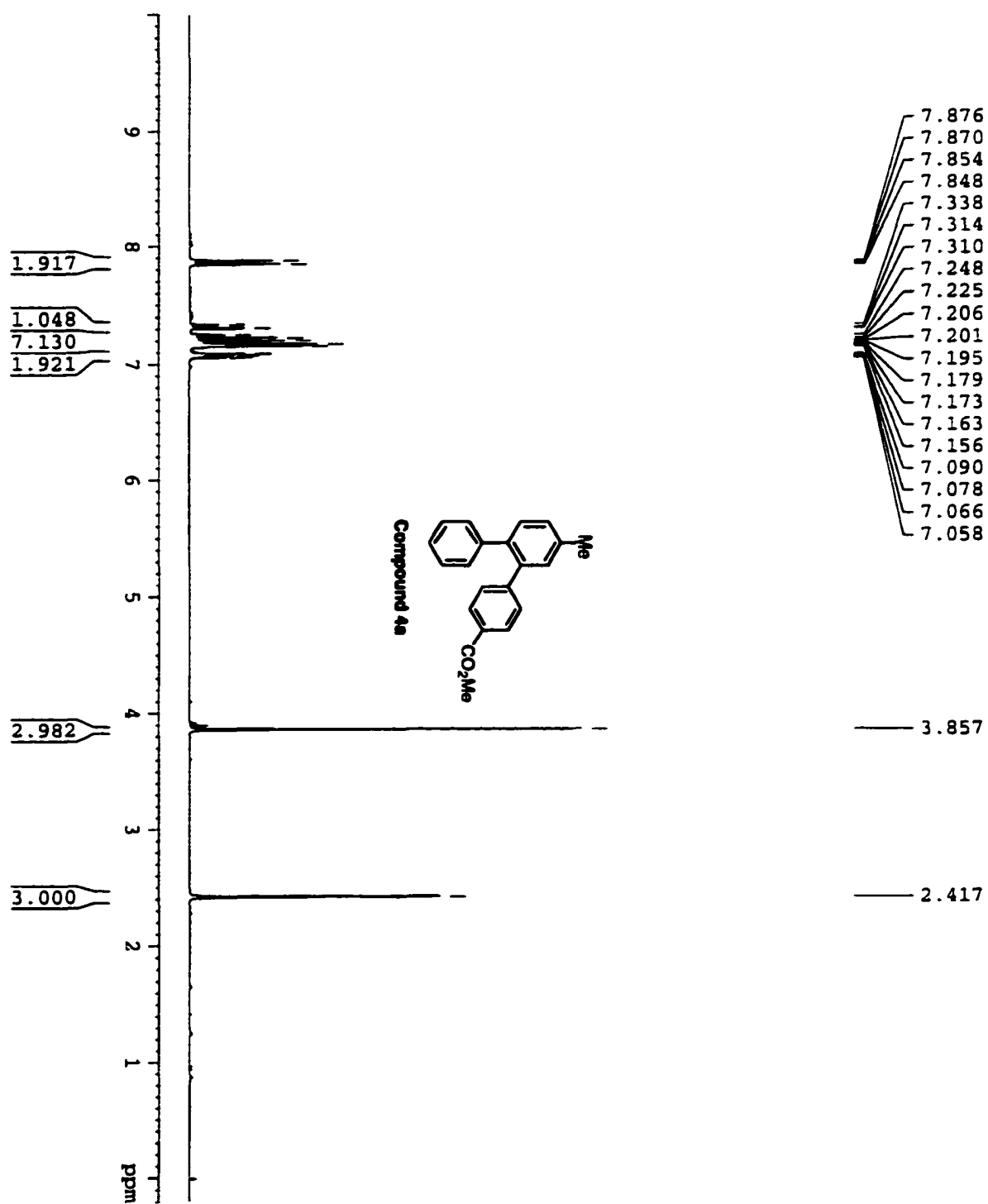


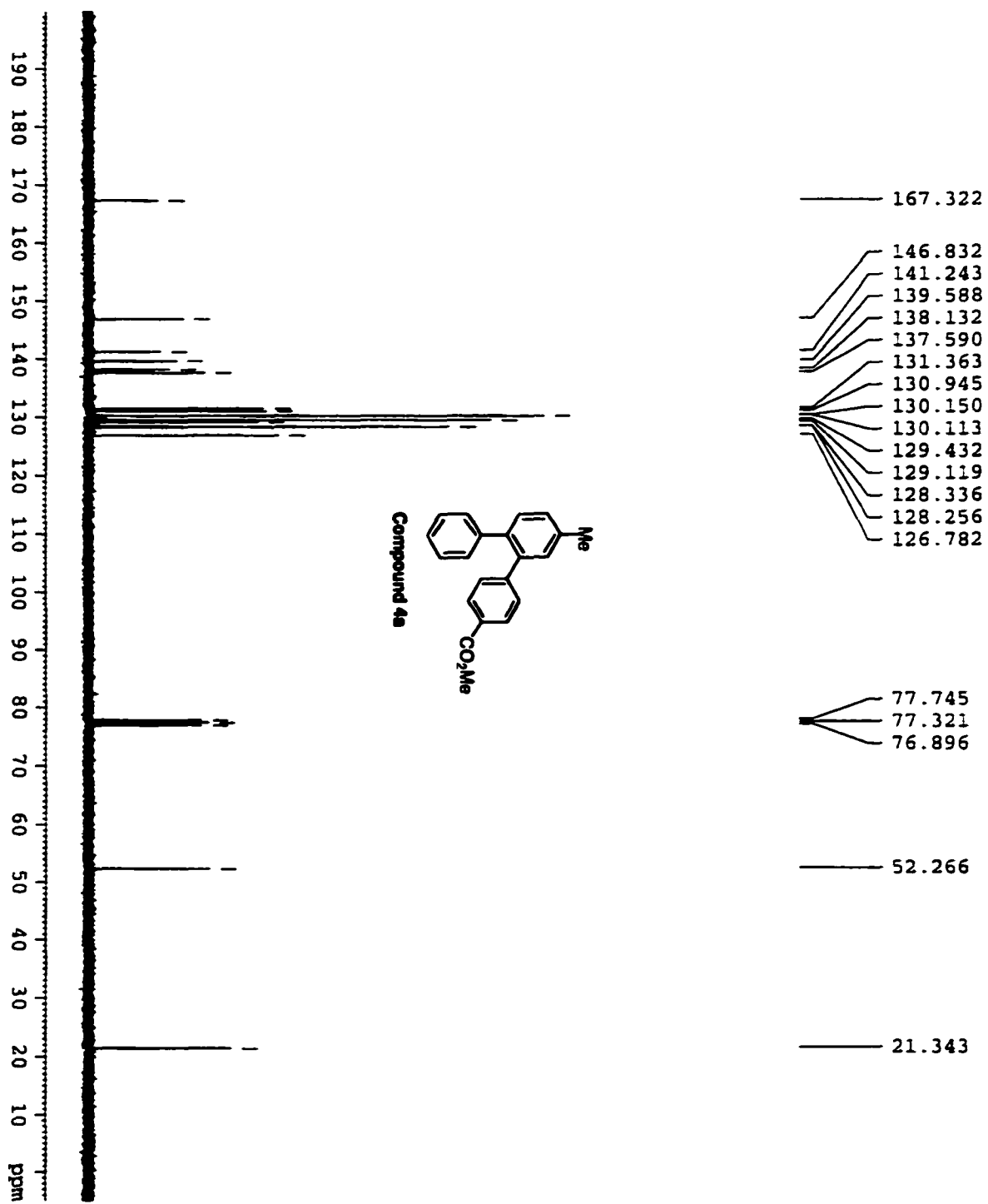


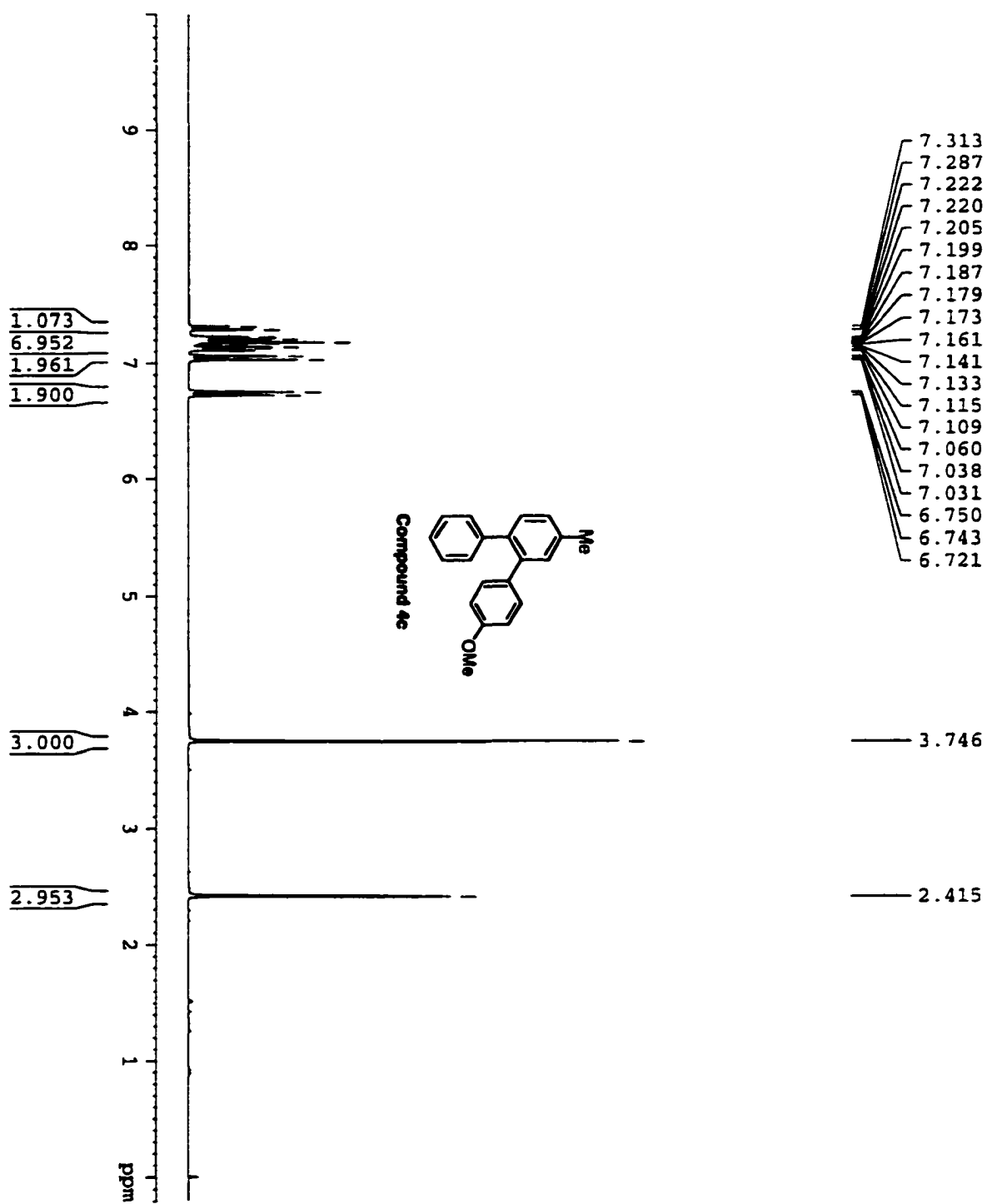




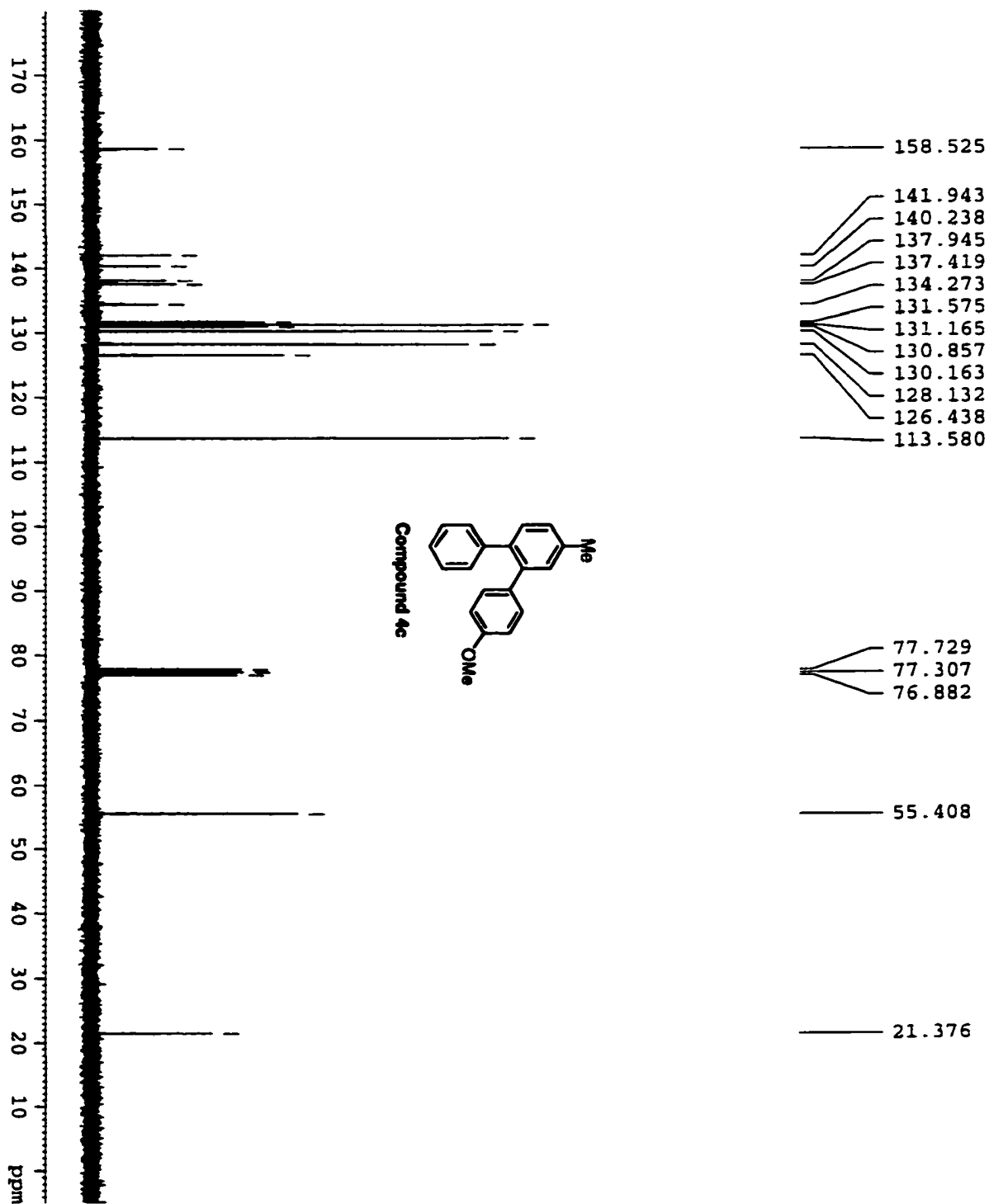


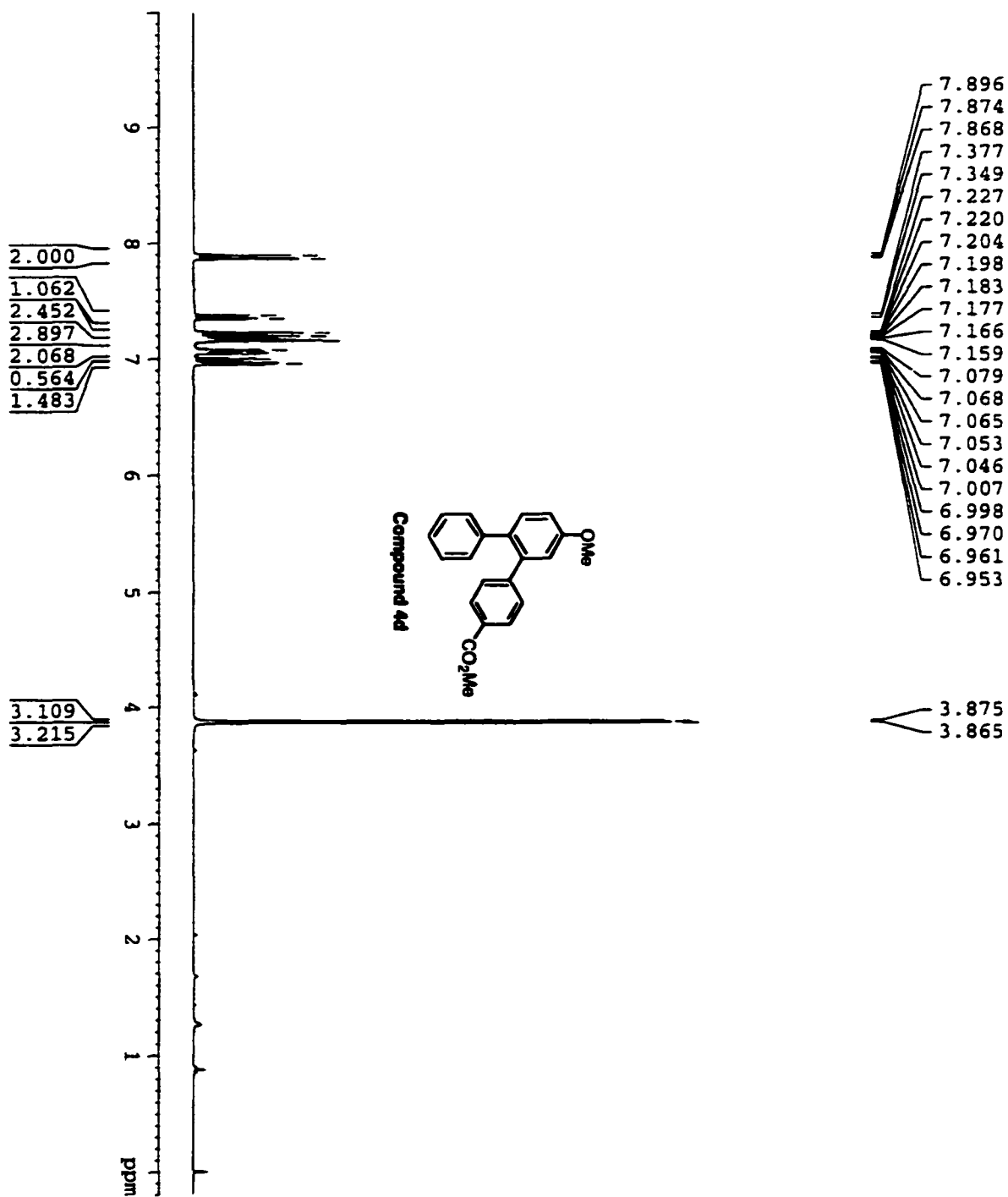


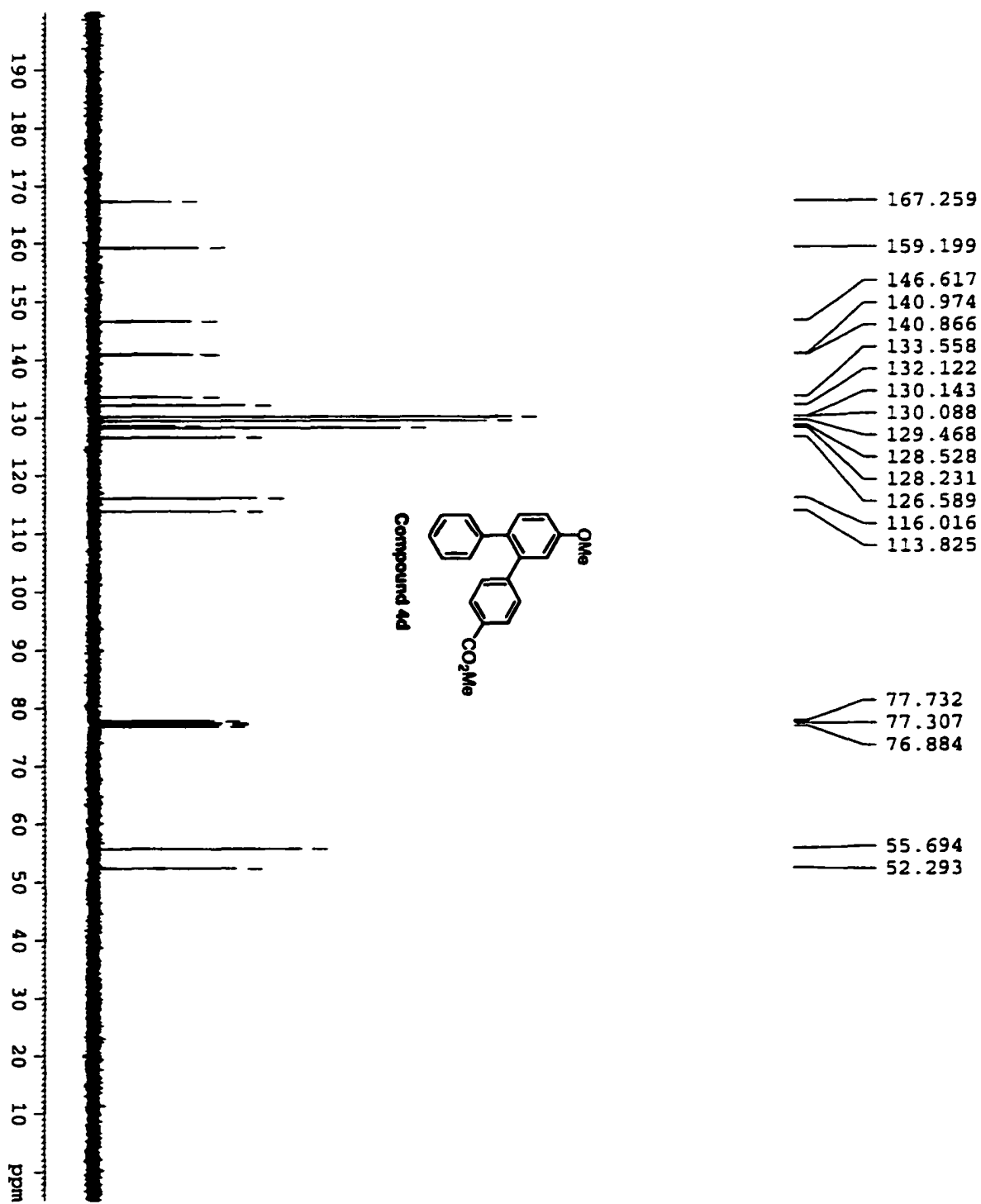


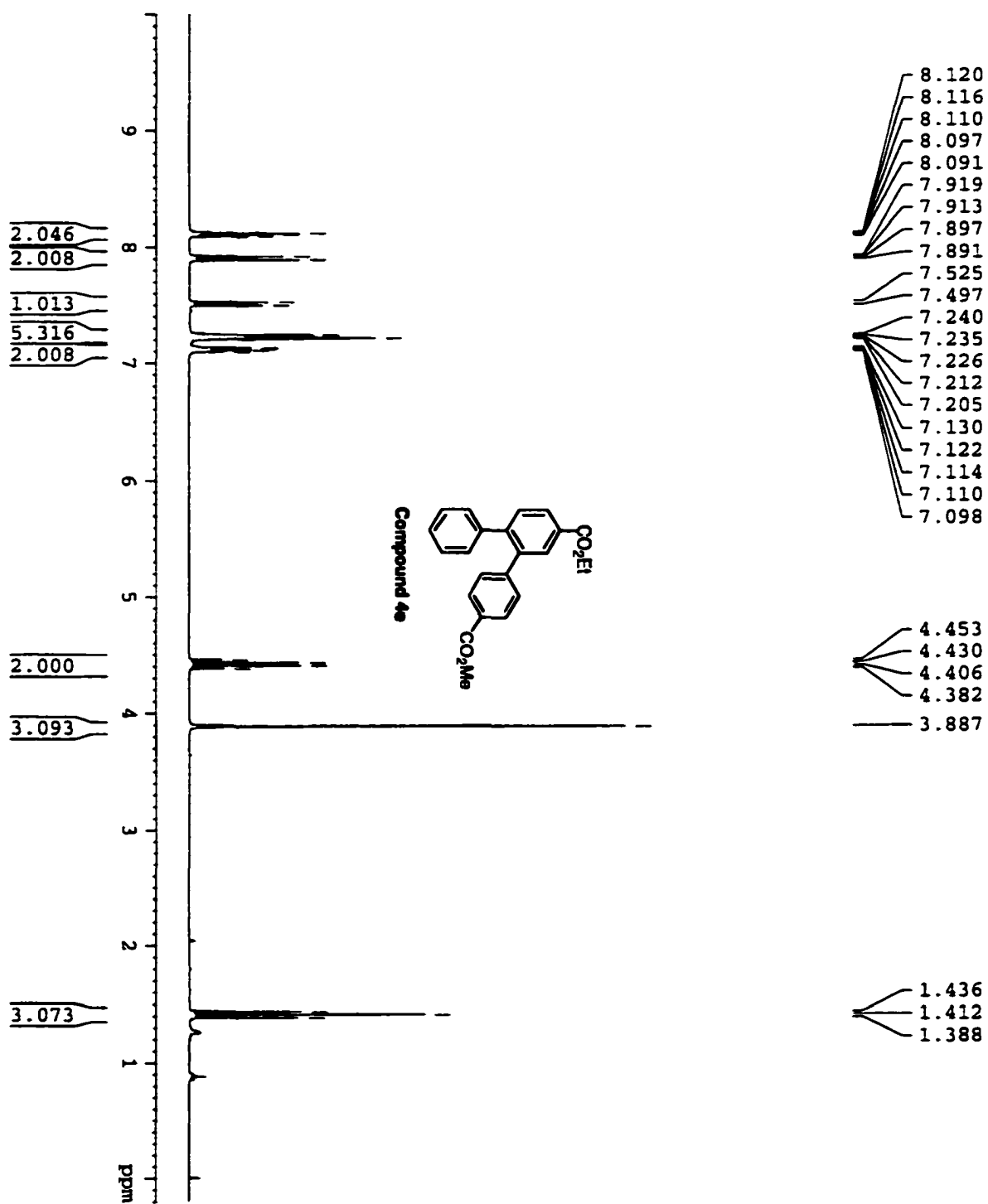


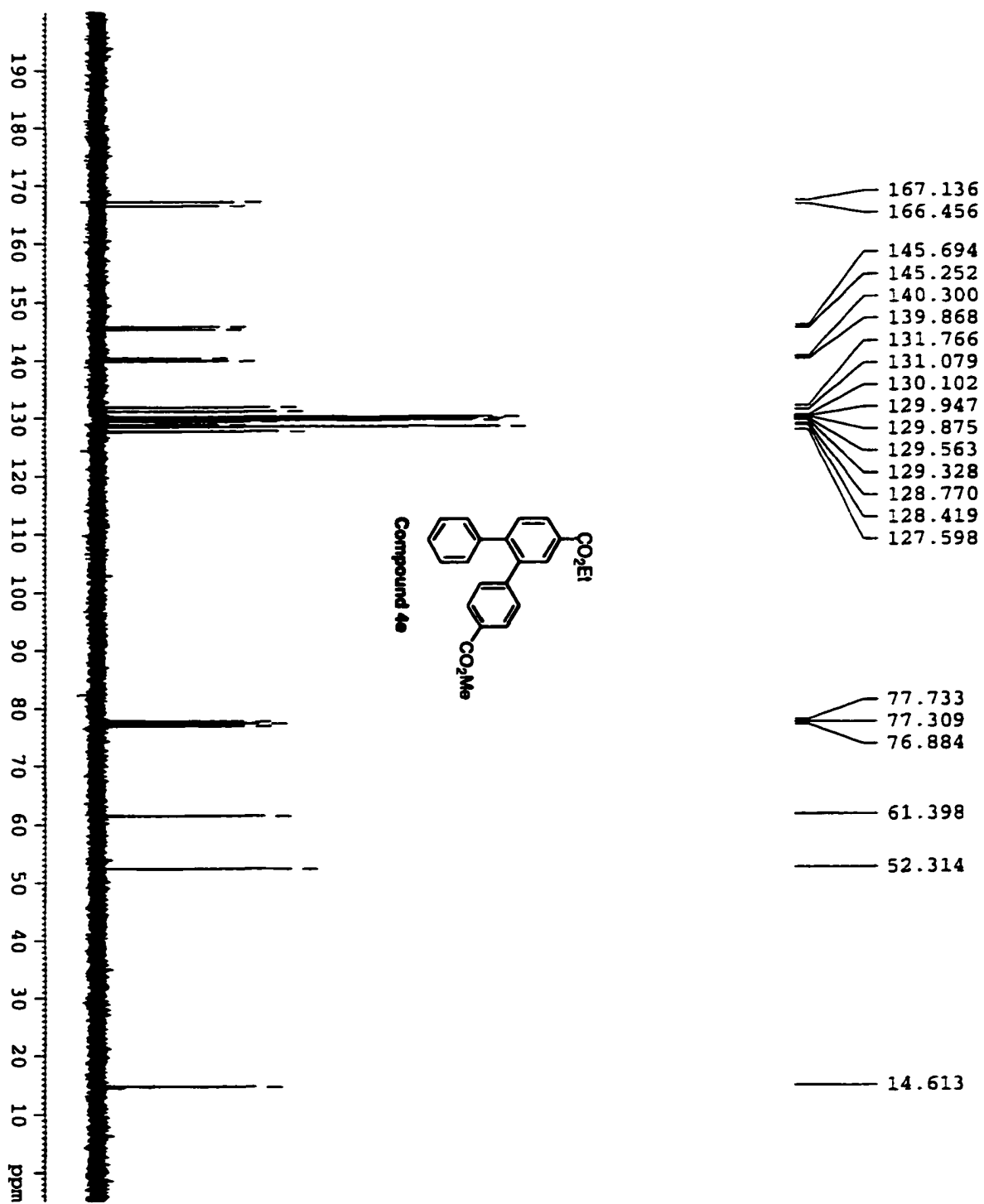


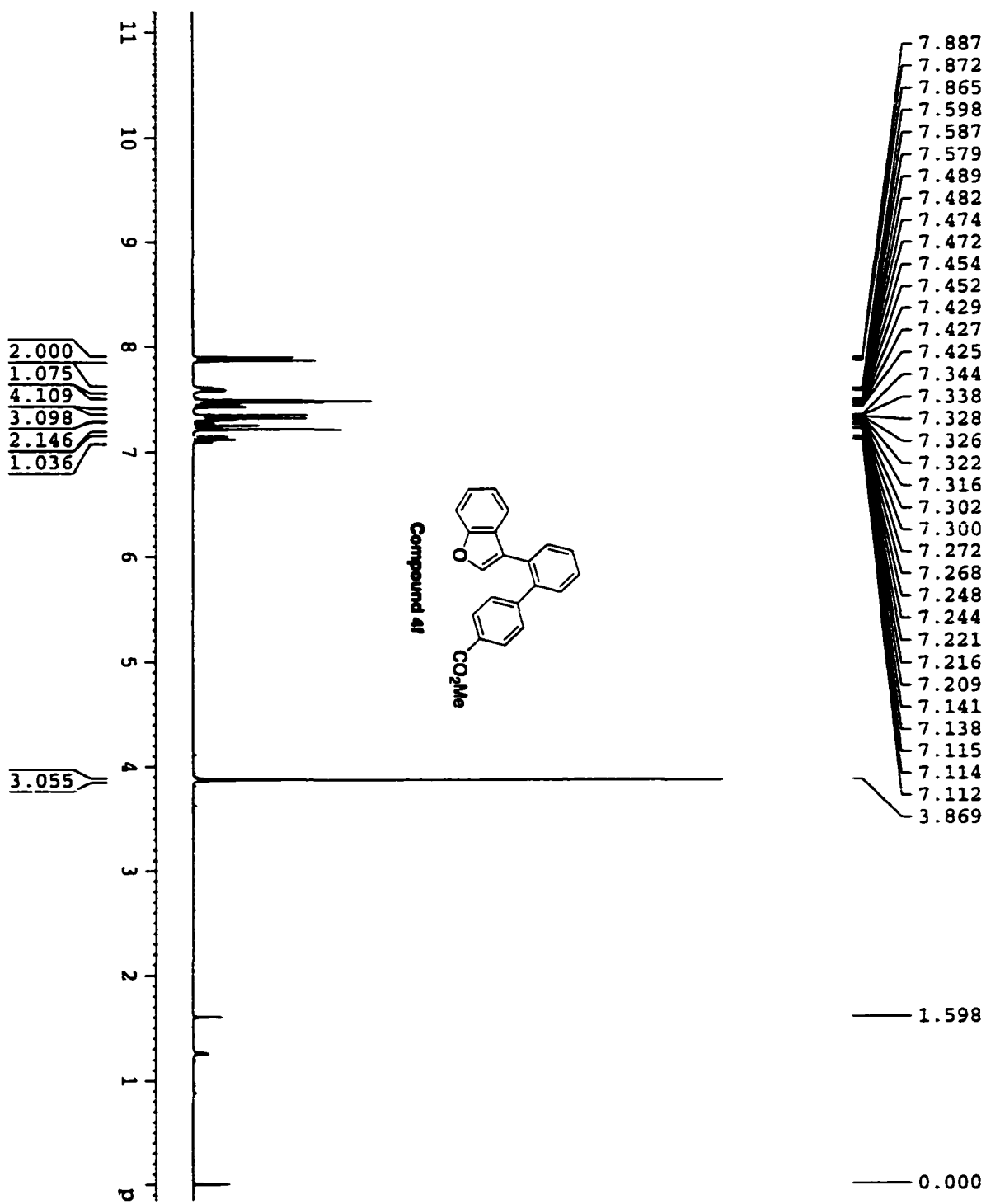


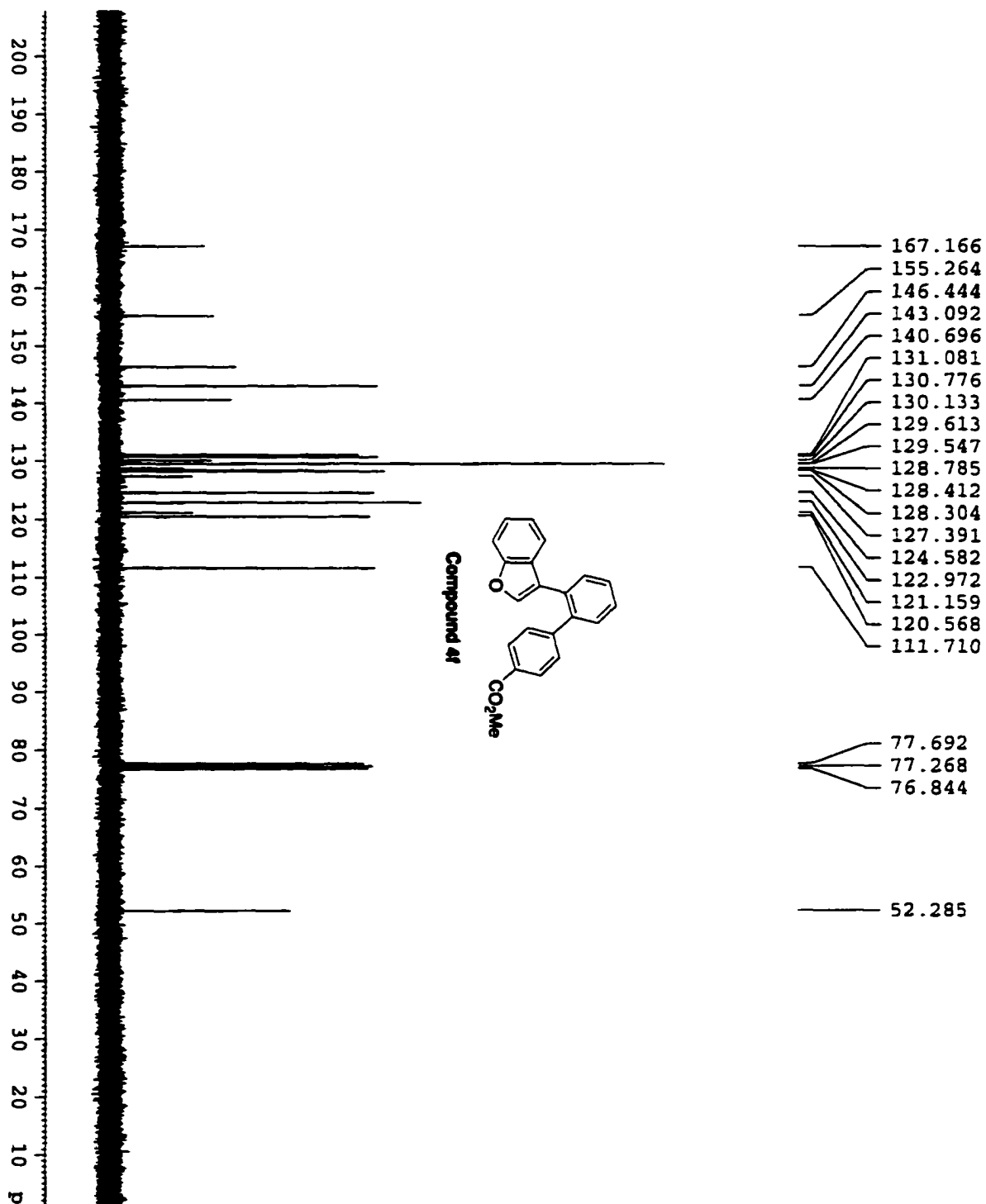


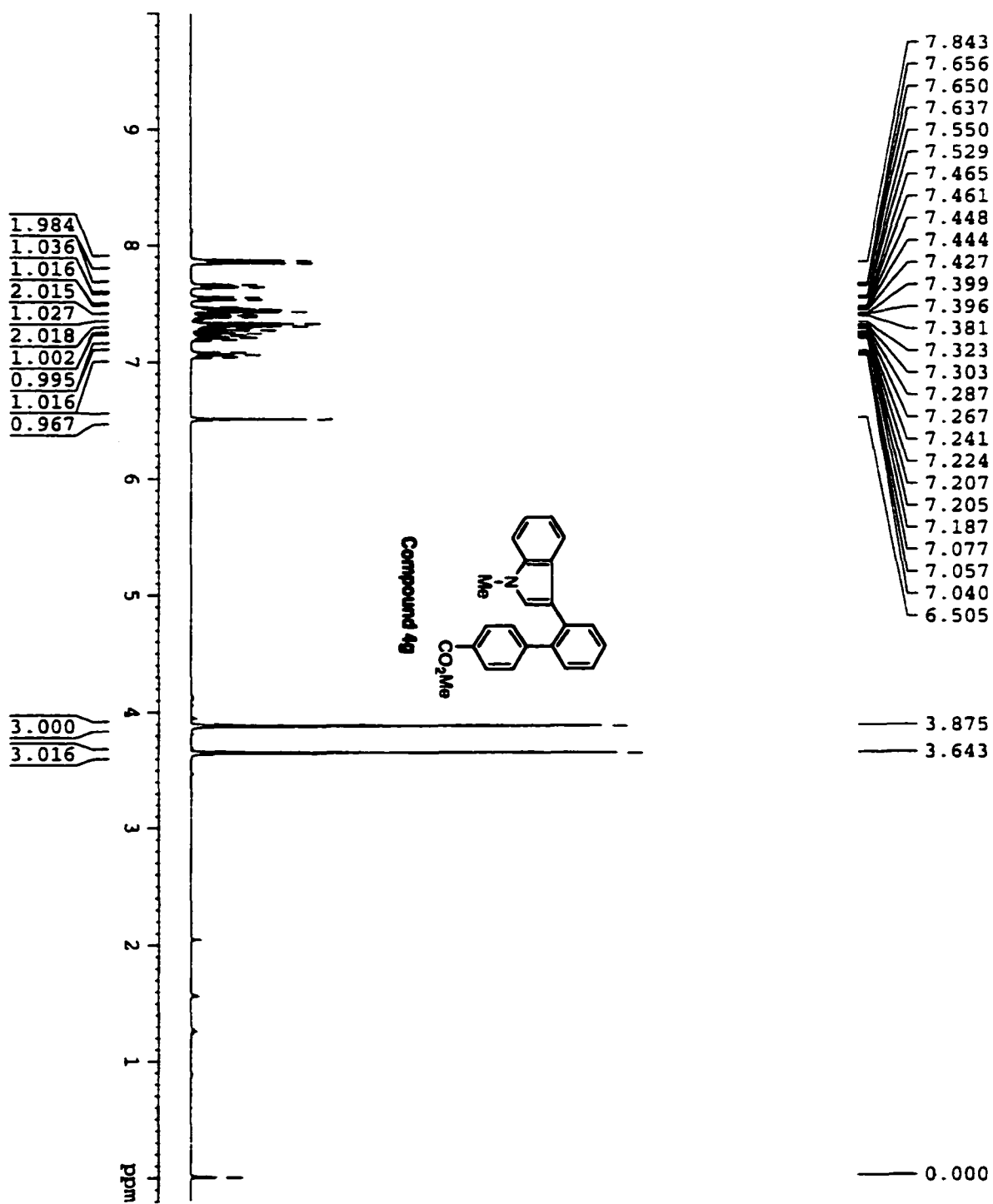




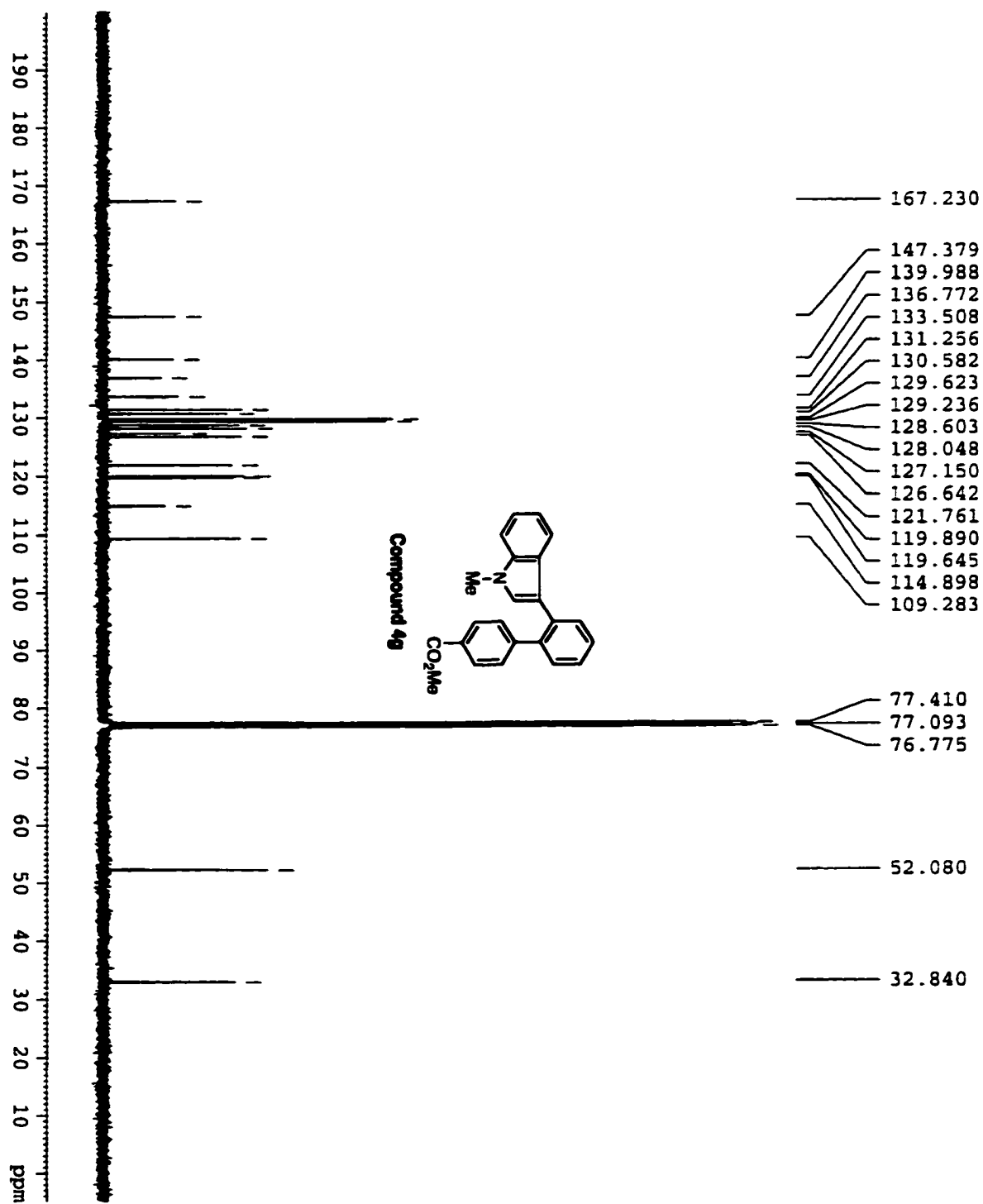


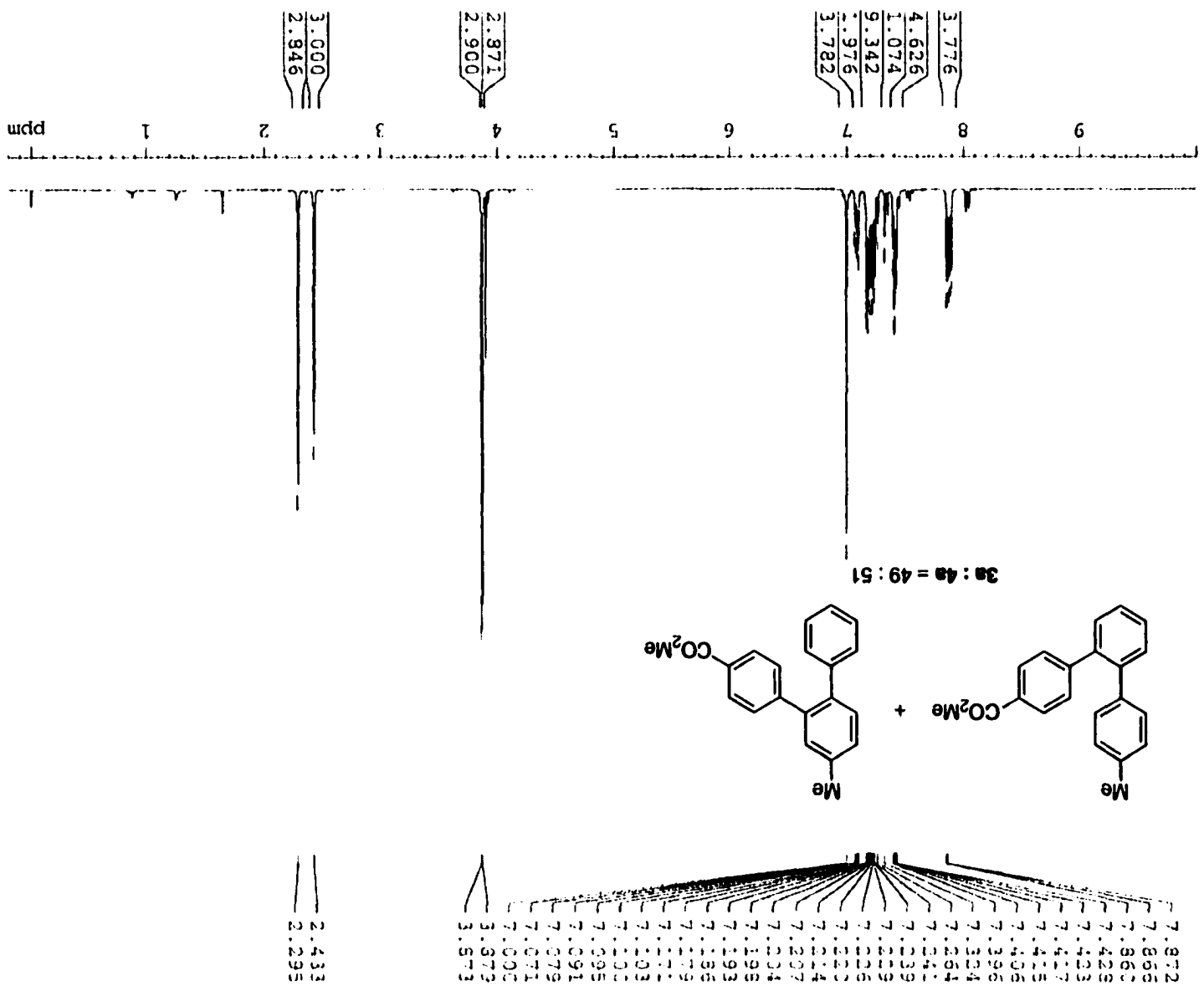


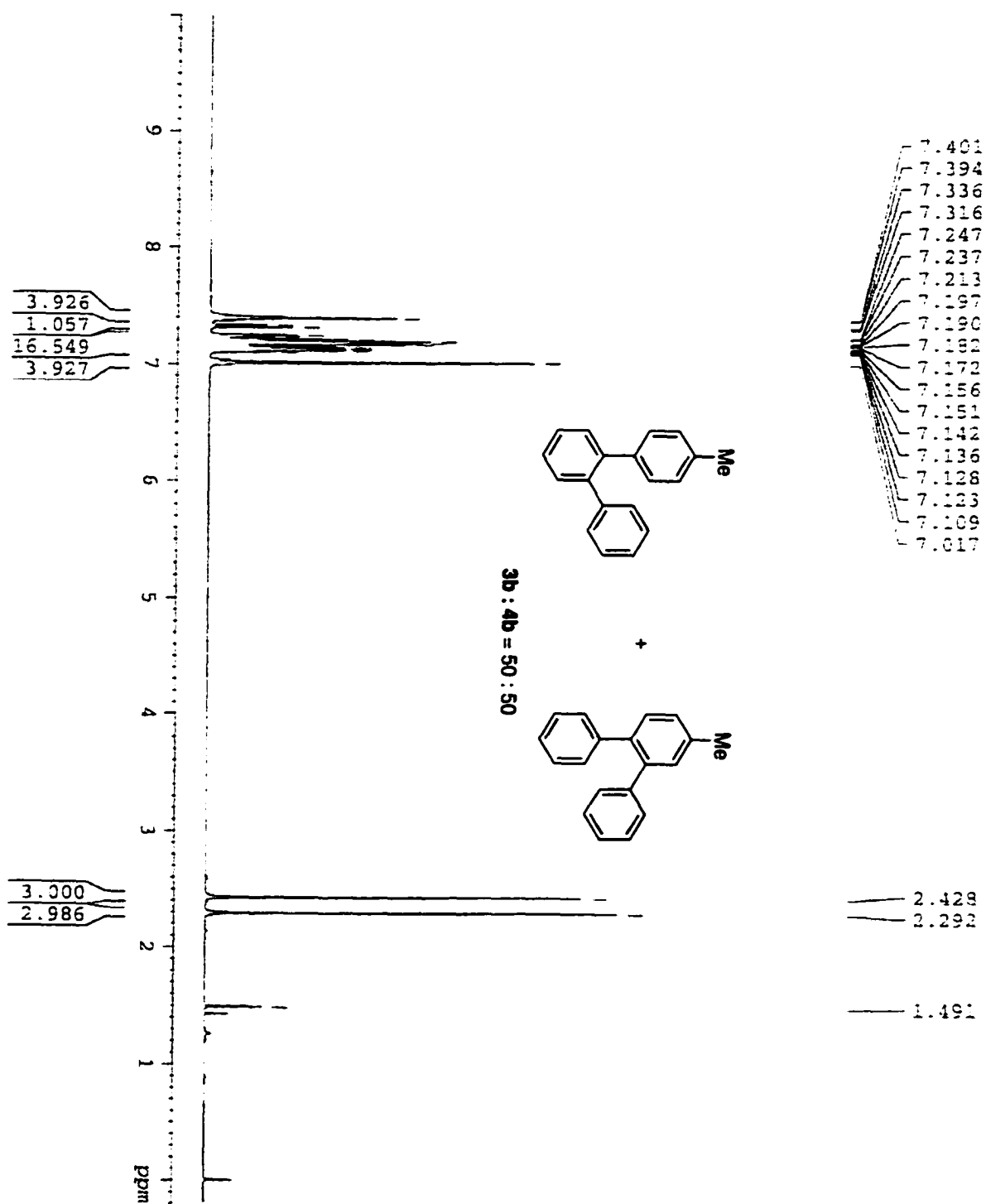














11	11
22	22
33	33
44	44
55	55
66	66
77	77
88	88
99	99

